Isotope Effect Studies of Elimination Reactions

By A. Fry
DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ARKANSAS, FAYETTEVILLE, ARKANSAS, U.S.A.; and DEPARTMENT OF CHEMISTRY, UNIVERSITY OF AUCKLAND, AUCKLAND, NEW ZEALAND

'Reaction mechanisms in general are elucidated in successive approximations. The relative timing of concerted bond changes should represent the next major stage in the study of several general reactions, of which elimination is one of the simplest. Up to the present only reconnaissance work on it has been done.'

1 Introduction

The above quotation[1] is the last paragraph of Sir Christopher Ingold's 1962 Faraday Lecture on the mechanism of the elimination reaction. In the past ten years substantial progress has been made in elucidating the timing of bonding changes in elimination reactions, and one of the most powerful tools in such studies has been the kinetic isotope effect. However, in many respects exploitation of this unique tool for activated complex study has barely scratched the surface of the possibilities. It is the purpose of this work to review what has been done in this area, and to attempt to show how the technique could be used in helping to answer some of the remaining questions about mechanisms of elimination reactions.

With a few minor exceptions and limitations, kinetic isotope effects, *i.e.* differences in rates of reaction for isotopic isomers, are to be expected *if and only if* there are bonding changes at the labelled atom in proceeding from reactants to the activated complex.[2] Relative magnitudes of isotope effects are related to the extent and type of bonding change. Using modern computer techniques and programs for evaluating vibrational frequencies of isotopic isomers,[2,3] it is now possible to make highly sophisticated calculations of the isotope effects to be expected from different activated-complex models. The results for these different models can be tested against experimental data, and the incorrect ones rejected. Two very powerful techniques which can greatly expand the usefulness of this approach are: (1) the measurement and calculation of isotope effects for reactants successively labelled at different positions in the molecule,[4] and (2) the measurement and calculation of isotope effects for reactions involving substrates

[1] C. K. Ingold, *Proc. Chem. Soc.*, 1962, 265.
[2] J. Bigeleisen, *J. Chem. Phys.*, 1949, **17**, 675; J. Bigeleisen and M. Wolfsberg, *Adv. Chem. Phys.*, 1958, **1**, 15; M. J. Stern and M. Wolfsberg, *J. Chem. Phys.*, 1966, **45**, 4105; L. Melander, 'Isotope Effects on Reaction Rates', Ronald Press Co., New York, 1960.
[3] M. Wolfsberg and M. J. Stern, *Pure Appl. Chem.*, 1964, **8**, 225, 325; J. H. Schachtschneider and R. G. Snyder, *Spectrochim. Acta*, 1963, **19**, 117.
[4] A. Fry, *Pure Appl. Chem.*, 1964, **8**, 409.

containing aromatic rings with various substituents.[5] Agreement between experiment and qualitative theory or calculated results may be obtained for many activated complex models when isotope effect results for a substrate labelled at only one position must be fitted, but when isotope effect results for a substrate labelled successively at several positions must agree with qualitative theory or calculated results, the number of acceptable activated complex models decreases dramatically. Further refinements in the activated complex model may be made by correlating changes in isotope effects with changing reaction mechanisms (changes in relative bonding or timing) as substituents on aromatic rings in the reacting system are changed. In view of the many atomic positions at which bonding changes take place, mechanisms of elimination reactions are particularly susceptible to attack by these two techniques but, as yet, neither has been exploited fully.

2 Primary Elimination Reaction Mechanisms—Isotope Effect Predictions

The primary mechanisms of elimination reactions are conveniently and traditionally considered in three broad mechanistic classes,[1,6-8] *E*1, *E*2, and *E*1cb. In principle, the various mechanisms are susceptible to distinction on the basis of isotope effect experimentation.[9] The questions of whether there are clear-cut dividing lines between the mechanistic classes can perhaps be best answered by isotope effect research. Mechanistic subtleties within the broad classes can be studied effectively using relative magnitudes of isotope effects for closely related compounds. For one charge type, the three primary mechanistic classes (other elimination reaction mechanisms will be considered in later sections) and their predicted isotope effect consequences are depicted below. The predictions are qualitative and are based on the assumption that isotopic substitution at (but not that 'remote' from) atomic positions undergoing bonding changes in the activation process will result in isotope effects. This assumption is solidly based on theory[2] (with some reservation about the definition of 'remote') but can also be utilized successfully on a more or less empirical basis.[4] For more precise predictions, recourse should be made to the type of detailed calculations mentioned above.

[5] For a recent application of this time honoured technique to isotope effect experiments, see B. W. Palmer and A. Fry, *J. Amer. Chem. Soc.*, 1970, **92**, 2580.

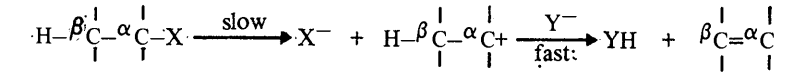
[6] W. H. Saunders, jun., 'Elimination Reactions in Solution', in 'The Chemistry of Alkenes', ed. S. Patai, Interscience Publishers, New York, 1964, p. 149.

[7] D. V. Banthorp, 'Elimination Reactions', Elsevier Publishing Co., London, 1963.

[8] J. F. Bunnett, *Angew. Chem.*, 1962, **74**, 731 (*Angew. Chem. Internat. Edn.*, 1962, **1**, 225); *Surv. Progr. Chem.*, 1969, **5**, 53.

[9] Review sources which the author has found particularly useful in considering applications of isotope effect research in elimination (and other) reaction mechanism studies include references 1, 2, 6—8 and E. A. Halevi, *Progr. Phys. Org. Chem.*, 1963, **1**, 109; W. H. Saunders, jun., 'Kinetic Isotope Effects', in S. L. Friess, E. S. Lewis, and A. Weissberger 'Investigation of Rates and Mechanisms of Reactions', 2nd edn., Interscience Publishers, New York, 1961, Vol. 8, Part 1, p. 389; W. H. Saunders, jun., *Surv. Progr. Chem.*, 1966, **3**, 109; H. Simon and D. Palm, *Angew. Chem. Internat. Edn.*, 1966, **5**, 920; A. Streitwieser, jun., 'Solvolytic Displacement Reactions', McGraw-Hill Book Co., New York, 1962; E. R. Thornton, 'Solvolysis Mechanisms', Ronald Press Co., New York, 1964; and K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713. In addition, appropriate sections in *Ann. Reports* and *Ann. Rev. Phys. Chem.* are very helpful.

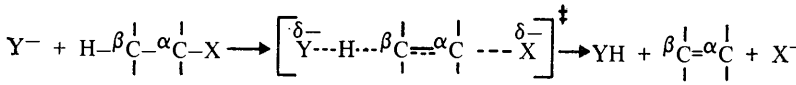
A. Carbonium Ion Mechanism, *E*1.—Primary[10] kinetic isotope effects would be



(1)

expected for labelled X and α-carbon, but not for labelled β-carbon or for α- or β-hydrogens. Secondary[10] hydrogen isotope effects would be expected for α-hydrogens and for properly oriented β-hydrogens. Carbonium ion (1) is a reactive intermediate, and there should be no measurable β-carbon or α- or β-hydrogen isotope effect on the overall rate in its decomposition to the elimination product.[11] In the event that reaction of (1) with Y^- has an appreciable activation energy, there should be an isotope effect (small, or perhaps even inverse since bond formation is involved) for labelled Y^-.

B. Concerted Mechanism, *E*2.—Primary kinetic isotope effects would be ex-

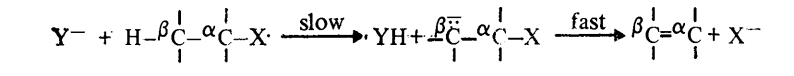


(2)

pected for labelled Y^-, β-carbon, α-carbon, X, and the eliminated β-hydrogen. Secondary isotope effects might be found for the α-hydrogens and the non-eliminated β-hydrogens.

C. Carbanion Mechanism, *E*1cb.—For the *E*1cb mechanism, two limiting types

Type A



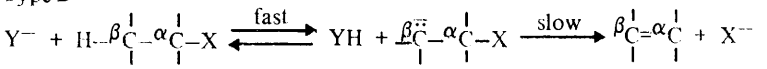
(3)

[10] Primary isotope effects are those observed for cases where a bond to the labelled atom is being broken or formed in the rate-determining step. Secondary isotope effects are those observed for cases where formal bond rupture or bond formation at the labelled position is not involved, but where bonding at the labelled atom is altered (as by hybridization changes, hyperconjugation, non-bonded steric interaction changes, *etc.*) in the rate-determining step. As we shall see, it is difficult to distinguish between certain primary and secondary isotope effects, especially for some β-hydrogen isotope effects in elimination reactions.

[11] Any isotope effects involved in further reactions of a reactive intermediate would not affect the overall rate of an irreversible reaction since, by definition, such an intermediate can only decompose to products. However, if there is a partition of a reactive intermediate among paths (including internal return) having different isotope effects, the product ratios will be altered by the presence of the isotope or, in a competitive experiment, some products will be enriched and others depleted in the isotope. For an example of such an *E*1–S_N1 partition see G. J. Frisone and E. R. Thornton, *J. Amer. Chem. Soc.*, 1968, **90**, 1211.

should be considered. If formation of carbanion (3) is rate-determining (type A), primary kinetic isotope effects would be expected for labelled Y^-, β-carbon, and β-hydrogens. Whether secondary isotope effects are to be expected for the non-eliminated β-hydrogens or the α-hydrogens would probably depend on the change in β-carbon hybridization. There should be no measurable isotope effects on the overall rate for labelled α-carbon or X as reactive intermediate (3) is converted to products.[11] Alternatively, if formation of carbanion (3) is rapid and reversible and its conversion to products is rate-determining (type B), primary kinetic isotope effects should be observed for labelled

Type B



(3)

X, α-carbon, and β-carbon, and equilibrium isotope effects could be measured for labelled Y^- and the β-hydrogens. Again, a secondary isotope effect might be observed for labelled α-hydrogens.

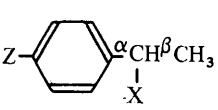
The fact that the *E*2 'mechanism' is really a whole spectrum of mechanisms with varying degrees of fractional bonding among X, α-C, β-C, Y^-, and β-H has been pointed out in a particularly clear fashion by Bunnett.[8] It is easy to visualize a version of (2) which would look very much like (3) and which would be the most *E*1cb-like of the *E*2 mechanisms. Similarly, one could visualize bonding in (2) which would place its structure very close to that of (1) (assuming placement of X^- near α-C and of Y^- or a nucleophilic solvent near the β-H). The isotope effect technique, using substrates labelled successively in various positions, is probably the most effective tool available for placing the mechanism of a particular reaction at a given point in the mechanistic spectrum. In the discussion below, particular attention will be given to what can be learned about the borderline mechanistic areas by isotope effect techniques. The isotope effect results available for reactions occurring by the various primary mechanisms will be taken up in the order *E*1, *E*1cb, *E*2.

All elimination reactions are accompanied, to a greater or lesser degree, by competing substitution (and sometimes other) reactions, and this can give rise to serious problems in isotope effect studies, especially for labelled α-C and X. A changed isotopic composition of a substrate due to an isotope effect in a competing reaction may give a 'false' isotope effect in the elimination reaction. For instance, if an elimination reaction were to go by the *E*1cb mechanism with rate-determining carbanion formation (type A) no isotope effect should be observed for labelled α-C. But if there is a normal isotope effect for labelled α-C in a competing S_N2 reaction, the substrate will be enriched in the heavy α-C isotope during the initial stages of the reaction and this fractionation should be reflected in an enrichment of the heavy α-C isotope in the elimination products giving a 'false' normal isotope effect if the calculation is based on recovered

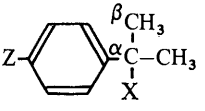
starting material, or a 'false' inverse isotope effect if the calculation is based on elimination products (see also reference note 11).

3 Isotope Effect Studies of *E*1 Reactions

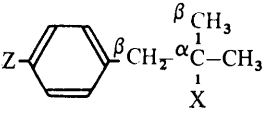
A. Labelled β-Carbon.—The most critical isotope-effect distinction at the borderline between the *E*1 and *E*2 mechanisms is whether or not there is an isotope effect for a compound with β-C labelled; for the *E*2 mechanism there should be an isotope effect, whereas for the *E*1 mechanism there should not. Unfortunately, no such experiment has been carried out on a compound for which the mechanism is thought to be *E*1 or on the borderline between *E*1 and *E*2. The *only* isotope effect study of an elimination reaction in which β-C is labelled is that of Simon and Mullhofer[12] who found $k^{12}/k^{14} = 1{\cdot}036$ for the pyrolysis at 51 °C of n-propyl-[2-^{14}C]-trimethylammonium hydroxide. Clearly, as expected, this is an *E*2 and not an *E*1 reaction. It would be interesting to search for possible isotope effects in the elimination reactions of β-C-labelled 1-phenylethyl (4), 2-phenyl-2-propyl (5), 2-phenyl-2-methyl-2-propyl (6), t-butyl (7), *etc.*, halides or toluene-*p*-sulphonates, where *E*1 or *E*1–*E*2 borderline reactions might be expected. Variation of the substituent Z might well influence the



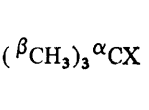
(4)



(5)



(6)



(7)

mechanisms of the reactions and the magnitudes of any isotope effects found. α- and/or β-hydrogen isotope effect measurements have been carried out on all of the above systems (see below).

B. Labelled X.—In principle, almost all the kinetic and kinetic isotope-effect research in solvolytic reactions which have been suggested to have carbonium ion intermediates is pertinent to the study of the *E*1 elimination reaction. In practice, in a large fraction of such studies, the products are not identified, and even when they are the emphasis is most frequently placed on the substitution products. In a qualitative sense, isotope effects are to be expected for both the *E*1 and *E*2 mechanisms for compounds labelled at X, α-C, or Y^-. Quantitatively, for labelled X, larger isotope effects are to be expected for *E*1 (complete $^{\alpha}$C—X bond rupture) than for *E*2 mechanisms ($^{\alpha}$C—X bond weakening). The few available studies give results in line with this conclusion, but much remains to be done before detailed mechanistic conclusions can be drawn. In the reaction

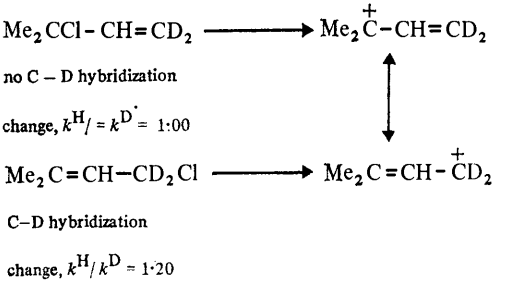
[12] H. Simon and G. Mullhofer, *Chem. Ber.*, 1963, **96**, 3167; *ibid.*, 1964, **97**, 2202; *Pure Appl. Chem.*, 1964, **8**, 379.

of t-butyl chloride with alcoholic silver nitrate,[13] the chlorine isotope effect, k^{35}/k^{37} = 1·0075, is in the S_N1 range (1·0075—1·0081) rather than the S_N2 range (1·0057—1·0058), established by Hill and Fry[14] for displacement reactions of substituted benzyl chlorides. Saunders and Zimmerman[15] compared the sulphur isotope effect for the uncatalysed, k^{32}/k^{34} = 1·0103, and ethoxide ion catalysed, k^{32}/k^{34} = 1·0072, decomposition of t-butyldimethylsulphonium iodide in ethanol. Presumably, there is complete rupture of the $^{\alpha}$C—S bond to form a carbonium ion intermediate in the uncatalysed case, but in the *E*2 reaction catalysed by ethoxide ion the $^{\alpha}$C—S bond is weakened but not broken. However, there may be some question about whether a carbonium ion is formed in the former case, since t-butyldimethylsulphonium iodide had earlier given[16] a substantially higher sulphur isotope effect, k^{32}/k^{34} = 1·0177, in a reaction with hydroxide ion in water. If the $^{\alpha}$C—S bond were completely broken in both cases, why should the isotope effects be different? Perhaps the answer lies in rupture of stronger sulphur–solvent solvation bonds in water than in ethanol on going from the positively charged sulphur in the ion to neutral dimethyl sulphide. Saunders and Katz[17] have reported some calculations of sulphur, nitrogen, and deuterium isotope effects for various mechanistic models. Measurements of chlorine and/or sulphur isotope effects for elimination reactions of a series of *p*-substituted 1-phenylethyl chlorides or dimethylsulphonium salts might provide valuable information about the *E*1–*E*2 mechanistic borderline region.

C. Labelled α-Carbon or Y$^-$.—Predictions about differences in magnitudes of isotope effects for α-C and Y$^-$ labelled compounds reacting by *E*1 or *E*2 mechanisms are less clear and experimental data are very sparse. No experimental isotope effect measurements for labelled Y in elimination reactions *of any kind* have been reported. Several quite large (k^{12}/k^{14} = 1·05—1·08) isotope effects for labelled α-C compounds reacting by the *E*2 mechanism have been reported (see below). Solvolysis isotope effects for α-C labelled t-butyl chloride,[18] k^{12}/k^{14} = 1·027, and *p*-substituted-1-phenylethyl bromide,[19] k^{12}/k^{13} = 0·9995—1·0127, are uniformly lower than those for S_N2 reactions of the same compounds (k^{12}/k^{13} = 1·036 for the 1-phenylethyl bromides). All the measurements were made on substitution rather than elimination products, but it is quite probable that the elimination reaction trend would be the same. If so, measurement of isotope effects for α-C labelled compounds in suitable systems such as (4), (5), and (6) above could serve as a powerful probe for the *E*1–*E*2 mechanistic borderline.

[13] R. M. Bartholomew, F. Brown, and M. Lounsbury, *Nature*, 1954, **174**, 133; *Canad. J. Chem.*, 1954, **32**, 979.
[14] J. W. Hill and A. Fry, *J. Amer. Chem. Soc.*, 1962, **84**, 2763.
[15] W. H. Saunders, jun., and S. E. Zimmerman, *J. Amer. Chem. Soc.*, 1964, **86**, 3789.
[16] W. H. Saunders, jun., and S. Asperger, *J. Amer. Chem. Soc.*, 1957, **79**, 1612.
[17] W. H. Saunders, jun., *Chem. Ind.* (*London*), 1963, 1661; A. M. Katz and W. H. Saunders, jun., *J. Amer. Chem. Soc.*, 1969, **91**, 4469.
[18] M. L. Bender and G. J. Buist, *J. Amer. Chem. Soc.*, 1958, **80**, 4304.
[19] J. Bron and J. B. Stothers, *Canad. J. Chem.*, 1969, **47**, 2506, and earlier papers in the series cited there.

D. Labelled α-Hydrogen.—The magnitude of the α-hydrogen isotope effect may be a very useful criterion of the degree to which α-C has changed from sp^3 to sp^2 hybridization in carbonium ion formation in the $E1$–S_N1 mechanism or in incipient double bond formation in the $E2$ mechanism. The generally accepted[9] origin of the α-hydrogen isotope effect is the relaxation of bonding (mainly involving H—$^{\alpha}$C bending frequencies) in going from the sp^3 hybridized reactant to the near sp^2 hybridized transition state. An ingenious demonstration of this concept is provided by Belanic-Lipovac, Borcic, and Sunko[20] in their studies on isomeric allylic chlorides:



In recent reviews[21,22] of the many reports on α-hydrogen isotope effects in solvolysis and other substitution reactions, S_N1–$E1$ reactions are shown to have large ($k^H/k^D \sim 1{\cdot}15$ at 25 °C) α-hydrogen isotope effects, characteristic of significant weakening of the $^{\alpha}$C—H bonding in the activation process. S_N2 reactions (and solvolysis reactions of primary halides or tosylates), on the other hand, showed α-hydrogen isotope effects ranging from small 'inverse' ($k^H/k^D < 1$, strengthened $^{\alpha}$C—H bonding in a 'tight' activated complex) to small 'normal' values ($k^H/k^D > 1$, weakened $^{\alpha}$C—H bonding in a 'loose' activated complex). On the basis of recent work,[23] which demonstrates that the main differences in α-hydrogen isotope effects in limiting S_N1–$E1$ reactions are due to differences in H$^{\alpha}$CX bending force constants in the reactants, it is now possible to say with considerable assurance that elimination (or substitution) reactions which have α-hydrogen isotope effects significantly different from the limiting values (at 25 °C, $k^H/k^D \sim 1{\cdot}22$ for X = F; $\sim 1{\cdot}15$ for X = Cl; $\sim 1{\cdot}125$ for X = Br; $\sim 1{\cdot}09$ for X = I; and $\sim 1{\cdot}22$ for X = OTs[24]) must have, at least in part, mechanisms different from $E1$ (or S_N1). In order to use these data in an effective manner in investigating the relationship between the $E1$ and $E2$ mechanisms, information on the magnitude of α-hydrogen isotope effects to be

[20] V. Belanic-Lipovac, S. Borcic, and D. E. Sunko, *Croat. Chem. Acta*, 1965, **37**, 61.
[21] S. Seltzer and A. A. Zavitas, *Canad. J. Chem.*, 1967, **45**, 2023.
[22] V. J. Shiner, jun., W. E. Buddenbaum, B. L. Murr, and G. Lamaty, *J. Amer. Chem. Soc.*, 1968, **90**, 418.
[23] V. J. Shiner, jun., M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *J. Amer. Chem. Soc.*, 1968, **90**, 7171.
[24] A. Streitwieser, jun., and A. G. Dafforn, *Tetrahedron Letters*, 1969, 1263.

expected in *E*2 reactions must be available. On the basis of the few measurements which have been made, it appears that *E*2 α-hydrogen isotope effects are small but perhaps sufficiently variable so as to serve as a useful mechanistic criterion. Using sodium ethoxide in alcohol, the following α-deuterium isotope effects have been reported: for isopropyl bromide,[25] no effect; for 2-phenylethyldimethylsulphonium bromide,[26] no effect (there was extensive exchange); for 2-phenylethyltrimethylammonium iodide,[26] a very small effect ($k^H/k^D > 1$); for 2-phenylethyl bromide,[26] $k^H/k^D = 1{\cdot}17$ (1·08 per deuterium); and for cyclohexyl tosylate,[27] $k^H/k^D = 1{\cdot}14$ (using potassium t-butoxide in t-butyl alcohol[27] $k^H/k^D = 1{\cdot}15$). In this last case the *E*2 α-hydrogen isotope effects are substantially smaller than that observed[28] in acetolysis of cyclohexyl toluene-*p*-sulphonate, where $k^H/k^D = 1{\cdot}22$. For the decomposition of n-propyl-[1-^{3}H]-trimethylammonium hydroxide in vacuum at 50 °C, the α-tritium isotope effect was found[11] to be small, $k^H/k^T = 1{\cdot}10$. Clearly, large α-hydrogen isotope effects are to be expected for *E*1 reactions. On the basis of the above limited data it is tempting to speculate that the reduction in the size of the α-hydrogen isotope effect from the *E*1 limiting value might be useful in evaluating the extent to which the $^{\alpha}$C—X bond is still intact at the *E*2 activated complex. But the situation is perhaps more complex in that a substantial α-hydrogen isotope effect would probably be expected for a reaction with a mechanism near the centre of the *E*2 range, where there is considerable double bond formation, *as well as* for an *E*2 reaction with a mechanism near the *E*1 border. More data on closely related *E*2 reactions, such as those of various *p*-substituted 2-phenethyl or 1,2-diphenylpropyl[29] derivatives, would be very useful in evaluating the usefulness of the α-hydrogen isotope effect as a criterion of elimination-reaction mechanism.

It is also of interest to note that magnitudes of α-hydrogen isotope effects may be of considerable value in estimating the type and degree of neighbouring group participation in S_N1–*E*1 solvolytic reactions. Such backside bonding is expected to lead to more restricted $^{\alpha}$C—H bending motions in the activated complex than in the reactants, and thus to reduced α-hydrogen isotope effects.[30]

E. Labelled β-Hydrogen.—By far the greatest number of isotope effect studies of elimination reactions have utilized compounds with the β-hydrogens labelled; a large fraction of these studies has been concerned with solvolytic S_N1–*E*1 reactions, often under conditions where there is little or no elimination, and often without specific attention to the elimination aspects of the overall reaction.

[25] V. J. Shiner, jun., *J. Amer. Chem. Soc.*, 1952, **74**, 5285.
[26] S. Asperger, N. Ilakovac, and D. Pavlovic, *J. Amer. Chem. Soc.*, 1961, **83**, 5032; *Croat. Chem. Acta*, 1962, **34**, 7; S. Asperger, L. Klasinc, and D. Pavlovic, *ibid.*, 1964, **36**, 159.
[27] K. T. Finley and W. H. Saunders, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 898.
[28] W. H. Saunders, jun., and K. T. Finley, *J. Amer. Chem. Soc.*, 1965. **87**, 1384.
[29] See the discussion in ref. 8 (i.e. *Surv. Progr. Chem.*, 1969, **5**, 81).
[30] For leading references see ref. 9, A. Streitwieser, 'Solvolytic Displacement Reactions'; S. L. Loukas, M. R. Velkou, and G. A. Gregoriou, *Chem. Comm.*, 1970, 251; C. C. Lee and L. Noszko, *Canad. J. Chem.*, 1966, **44**, 2491; C. C. Lee and E. W. C. Wong, *J. Amer. Chem. Soc.*, 1964, **86**, 2752.

As far as primary isotope effects are concerned, β-hydrogen labelling should provide a clear distinction between the *E*1 (no primary effect) and *E*2 (definite primary effect) mechanisms. But since there are substantial secondary β-hydrogen isotope effects in *E*1–S_N1 reactions (see below), and since *E*2 primary β-hydrogen isotope effects change smoothly from small to large to small again as the degree of transfer of the β-hydrogen from β-C to Y^- increases,[31] it is impossible to use with assurance the magnitude of the β-hydrogen isotope effect as a distinctive criterion of mechanism at either the *E*1–*E*2 or the *E*2–*E*1cb borderline.

In solvolytic reactions of aliphatic tertiary and many secondary substrates, replacement of β-CH_3 by β-CD_3 causes a rate depression of about a third, $k^H/k^D \sim 1{\cdot}33$.[32,33] The effects are generally cumulative.[33,34] For solvolysis of other secondary and primary substrates the β-hydrogen isotope effects are much smaller.[35] For instance, for solvolysis in water, for the series ethyl bromide, isopropyl bromide, t-butyl chloride the k^H/k^D per CD_3 group values are 1·03 (60 °C), 1·15 (60 °C), and 1·37 (2 °C).[35] This reduction is thought to stem from increasing nucleophilic solvent involvement (S_N2-like) as the branching decreases, and points to carbonium ion character at α-C as being the important reason for the secondary β-hydrogen isotope effect.[36] The main mechanism through which the carbonium ion centre exerts its influence is almost certainly hyperconjugation (delocalization of the sp^3–s $^\beta$C—H σ-bond electrons into the developing α-C p orbital), resulting in 'looser' $^\beta$C—H bonding in the activated complex than in the reactants, and thus an isotope effect in the 'normal' direction.[37] The $^\beta$C—H σ-orbital and the developing p-orbital on α-C must be

[31] F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265; for more extensive calculations and leading references to recent work see R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1970, 785.

[32] Shiner and Lewis have summarised the notable early work of their research groups in this area, V. J. Shiner, jun., *Tetrahedron*, 1959, **5**, 243; E. S. Lewis, *ibid.*, 1959, **5**, 143. The early work of Streitwieser's group also deserves special mention, see A. Streitwieser, jun., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, 1958, **80**, 2326. Halevi's penetrating and critical review (ref. 9) is excellent.

[33] A frequently used and useful form for expressing such results on a per-hydrogen basis is $\Delta(\Delta F^\ddagger) = (RT/n)\log k^H/k^D$; alternatively, k^H/k^D for a substrate having n hydrogens replaced by deuteriums may be raised to the $1/n$ power.

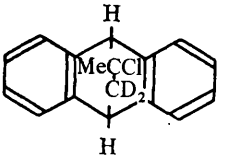
[34] V. J. Shiner, jun., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, 1963, **85**, 2413, and references cited therein.

[35] K. T. Leffek, J. A. Llewellyn, and R. E. Robertson, *Canad. J. Chem.*, 1960, **38**, 2171, and other earlier papers in the series cited there.

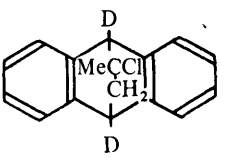
[36] In line with this, for some cases such as t-butyl chloride (ref. 11), these isotope effects are remarkably independent of solvent; for other cases, such as isopropyl tosylate, the nucleophilic involvement of the solvent shows up clearly: $k^H/k^D = 1{\cdot}55$ (1·24 per CD_3) *cf.* $k^H/k^D = 2{\cdot}12$ (1·45 per CD_3) for solvolysis in water (ref. 35) and trifluoroacetic acid (ref. 24). The low, $k^H/k^D = 1{\cdot}25$ (for the β-D_5 molecule), β-hydrogen isotope effect for solvolysis of t-amyldimethylsulphonium iodide is probably best explained by an activated complex with comparatively little carbonium ion character at α-C, with most of the positive charge still being on sulphur; S. Asperger and N. Ilakovac, *Chem. Ind.* (*London*), 1960, 1191

[37] A decrease in non-bonded interactions involving the β-hydrogens as the carbonium ion centre develops has been suggested (see, for example, H. C. Brown, M. E. Azzaro, J. G. Kelling, and G. J. McDonald, *J. Amer. Chem. Soc.*, 1966, **88**, 2520, for leading references) as the main cause for the β-hydrogen isotope effect. In the opinion of the author, the proponents of hyperconjugation have much the better of the argument, but, fundamentally, any detailed models from which calculations are made for comparison with experiment necessarily involve both molecular geometries and force constants, so, in a way, the question becomes moot (or perhaps better, subject to 'computer experiment' test).

parallel for maximum overlap (electron delocalisation), which leads to the conclusion that there should be conformational requirements for the β-hydrogen isotope effect. That this is indeed the case has been demonstrated in a most convincing manner by Shiner and co-workers.[32,38] Compound (8) undergoes *E*1–S_N1 solvolysis with k^H/k^D = 1·14, while its isotopic isomer (9), in which there can be no overlap of the $^{\beta}$C—D σ-orbital with the developing α-C *p*-orbital, has a k^H/k^D value of 0·986. It was even possible to tabulate contributions to the



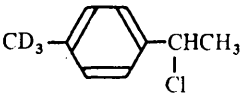
(8)



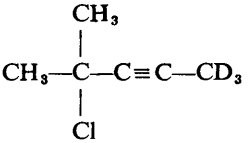
(9)

isotope effect by β-hydrogens in various different conformations relative to the α-C *p*-orbital.[38]

The existence of isotope effects for the *E*1–S_N1 solvolysis of compounds labelled in positions remote from α-C but conjugated with it by a benzene ring[32] or triple bond[39] also strongly supports the hyperconjugation explanation for β-hydrogen isotope effects.

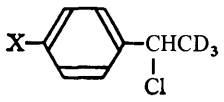


k^H/k^D = 1·08



k^H/k^D = 1·09

It might be expected that hyperconjugative stabilization of the developing positive charge on α-C would be less important, leading to a reduced β-hydrogen isotope effect, for a case where the positive centre is conjugated with a benzene ring, especially one containing an electron donating group. Such a study has been reported from Shiner's laboratory:[22]

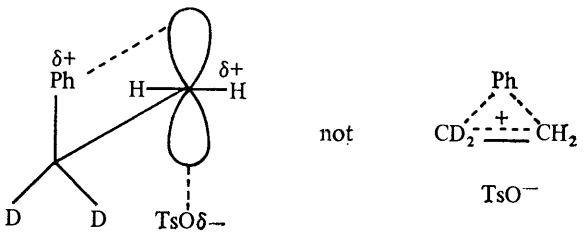


X	k^H/k^D
CH_3O	1·113
CH_3	1·200
H	1·224
NO_2	1·151

[38] V. J. Shiner, jun., and J. S. Humphrey, jun., *J. Amer. Chem. Soc.*, 1963, **85**, 2416.
[39] V. J. Shiner, jun., and G. S. Kriz, jun., *J. Amer. Chem. Soc.*, 1964, **86**, 2643.

The 'standard' β-hydrogen isotope effect per CD_3 group (t-butyl chloride data[34]) is $k^H/k^D = 1{\cdot}33$. All the above values are substantially lower, that for the strongly conjugated *p*-methoxy-compound being especially low, in accordance with the above suggestion. All the reactions, except that of the *p*-nitro compound, are S_N1–$E1$ on the basis of the α-hydrogen isotope effect classification given above.[22] Both the α- and β-isotope effects are decreased for the *p*-nitro-compound because of the incursion of substantial nucleophilic attack by the solvent on α-C.

Neighbouring phenyl participation in $E1$–S_N1 solvolysis reactions may also be studied by β-deuterium isotope effects. To the extent that neighbouring phenyl can supply electrons to the developing positive charge, a reduced isotope effect would be expected as described above. Furthermore, a bridged ion would freeze the molecule in a conformation unfavourable[38] for hyperconjugation (dihedral angles of 60° between the α-C *p*-orbital and the $^{\beta}$C—H bonds). For a symmetrical phenonium ion, to a first approximation at least, the α- and β-hydrogen isotope effects would be expected to be the same. On the basis of about normal α- and very low β-hydrogen isotope effects in the $E1$–S_N1 solvolysis of 2-phenylethyl tosylates, Saunders and co-workers[40] concluded that neighbouring phenyl participation did take place, but that the activated complex resembles reactant much more than a symmetrical phenonium ion. From the results of recent

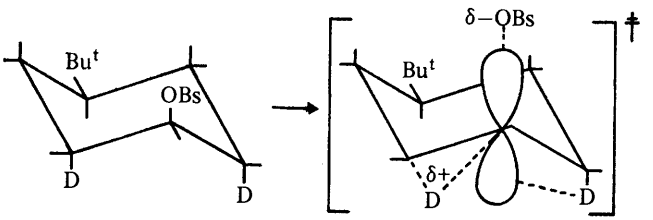


α- and β-hydrogen isotope-effect research by Loukas, Velkou, and Gregoriou[30] it appears that neighbouring phenyl participation in the 3-phenyl-2-butyl system may be very solvent dependent. At any rate, this is quite a complex system, and isotope effect research has excellent potential for making a meaningful mechanistic contribution.

In several $E1$–S_N1 solvolysis reactions,[41–43] the idea of β-hydrogen participation has been invoked to rationalize β-hydrogen isotope effects larger than those expected from the standard cumulative approach mentioned above.[34,38] For

[40] W. H. Saunders, jun., and R. Glaser, *J. Amer. Chem. Soc.*, 1960, **82**, 3586 and earlier work cited there; see also R. A. Sneen, R. W. Jenkins, jun., and F. L. Riddle, jun., *ibid.*, 1962, **84**, 1598.
[41] V. J. Shiner, jun., and J. G. Jewett, *J. Amer. Chem. Soc.*, 1965, **87**, 1382, 1383; 1964, **86**, 945; V. J. Shiner, jun., and J. O. Stoffer, *ibid.*, 1970, **92**, 3191.
[42] D. J. Cram and J. Tadanier, *J. Amer. Chem Soc.*, 1959, **81**, 2737.
[43] S. Winstein and J. Takahashi, *Tetrahedron*, 1958, **2**, 316.

instance, Shiner and Jewett,[41] in studying the solvolysis of *cis*-4-t-butylcyclohexyl brosylate, found that $k^H/k^D = 2{\cdot}565$ for the 2-equatorial-2,6-diaxial-D_3-compound, which is considerably larger than the expected value of 2·260 based on the monoequatorial-D (1·096) and monoaxial-D (1·436) values. The authors attribute the discrepancy to non-equivalence of the two axial hydrogens, one of them being involved in normal hyperconjugation with the positive centre, and the other forming an unsymmetrical hydrogen-bridge:

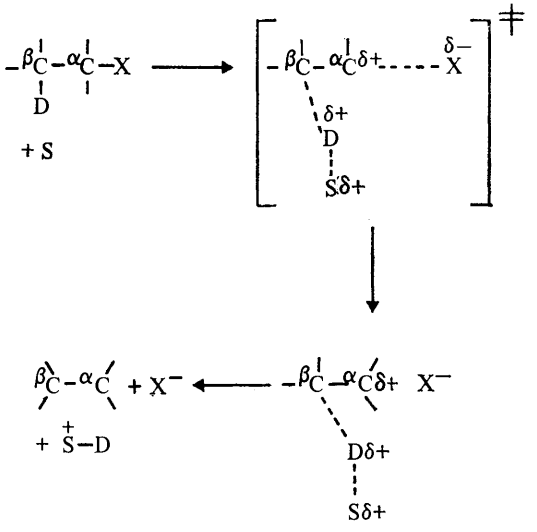


The neighbouring hydrogen participation is viewed 'as an extreme manifestation of a type of electronic interaction also associated with hyperconjugation'.

The elimination reaction predominates in the above reactions, and an alternative view which may have merit in some cases is to think of these solvolytic reactions as occupying the *E*1–*E*2 border with some small amount of $^{\beta}$C—H bond extension being caused by nucleophilic solvent attack on the β-hydrogen. This should give rise to a small *primary* isotope effect. In effect, as the β-hydrogen becomes more positive by hyperconjugative electron withdrawal from the $^{\beta}$C—H σ-bond, the role of a nearby solvent molecule would be changed from general solvation to specific weak covalent interaction. If an ion-pair intermediate is formed, the covalently bound solvent molecule would still be present; in any event, the next step of the reaction, the elimination proper, must involve such an interaction since the β-hydrogen must eventually be removed to the solvent. The geometry of the activated complex for such a mechanism need not be greatly different from that for neighbouring hydrogen participation. Indeed, steric factors permitting, the β-hydrogen would be expected to shift toward α-C, responding to the electron shift represented by hyperconjugation. It would seem that a good test for such a mechanism would be to study the β-hydrogen isotope effect in systems such as these as a function of the nucleophilicity of the solvent. In the solvolysis reactions of *erythro*- and *threo*-3-cyclohexyl-2-butyl toluene-*p*-sulphonates, Cram and Tadanier[42] found substantially higher β-hydrogen isotope effects in acetic acid than in the less nucleophilic formic acid, as would be expected for the suggested mechanism. A more extensive study of solvent effects on isotope effects for such systems might provide the definitive data needed.

		CH_3CO_2H	HCO_2H
c-C_6H_{11}	*erythro* k^H/k^D	2·10	1·73
CH_3—C—$CHCH_3$			
D OTs	*threo* k^H/k^D	1·87	1·54

Another similar but somewhat more conventional alternative view of $E1$–S_N1 solvolytic reactions with 'abnormally high' β-hydrogen isotope effects is to consider them to involve recombination of the carbonium-ion–anion ion pair to

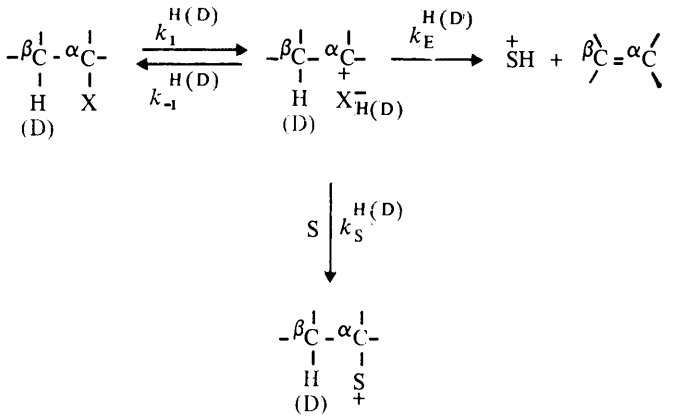


Ion pair

reactants, in kinetically significant competition with β-hydrogen abstraction by solvent to form olefin. The latter process would, of course, involve a primary β-hydrogen isotope effect, and this, in the usual steady-state treatment of such a system, would be reflected back into an overall reaction rate showing an 'abnormally high' isotope effect. Such ion pair recombination can sometimes be detected by common-ion rate depression or, better, by isotopic or other exchange experiments. A proposal of this sort has been made by Shiner's group (and discounted by others)[44] to explain the high value of the isotope effect in the $E1$–S_N1 solvolysis of [$^2H_9$]t-butyl chloride in trifluoroethanol. Similarly, Smith and Goon[45] have interpreted their β-hydrogen isotope effect results in the

[44] V. J. Shiner, jun., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, 1969, **91**, 4348; (and the contrary view) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v.R. Schleyer, *ibid.*, 1970, **92**, 5977.
[45] S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, 1969, **34**, 3127.

solvolysis of phenyldimethylcarbinyl chloride, *p*-nitrobenzoate, and thionobenzoate in this way. This idea may be conveniently examined using the usual mechanistic formulation:



Neglecting substitution for simplification of illustration (assuming a case where olefin formation predominates greatly, $k_E \gg k_S$) and using the usual steady-state treatment on the unlabelled compound, it is found that

$$k_{obs}^{H} = \frac{k_1^{H} k_E^{H}}{(X_H^-)(k_{-1}^{H}/k_E^{H}) + 1}$$

Applying the same treatment to the labelled compound, defining the ratio of ion recombination to olefin formation for the unlabelled compound as $k_{-1}^{H}/k_E^{H} = \epsilon$ (similar to the solvolysis mass-law constant α), and dividing one equation by the other leads to equation (1):

$$\frac{k_{obs}^{H}}{k_{obs}^{D}} = \frac{k_1^{H}}{k_1^{D}} \frac{k_E^{H}}{k_E^{D}} \left[\frac{k_E^{D}/k_E^{H} + \epsilon (X_D^-) k_{-1}^{D} k_{-1}^{H}}{1 + \epsilon (X_H^-)} \right] \qquad (1)$$

The ratio k_1^{H}/k_1^{D} for a limiting solvolysis reaction of phenyldimethylmethyl—CD_3 derivatives is probably not much different from that of 1-phenethyl—CD_3 compounds,[22] ~1·22 at 25 °C. The value of k_E^{H}/k_E^{D} may be evaluated directly by olefin analysis to determine the ratio of elimination into the CH_3 branch [to give $PhC(CD_3)=CH_2$] to elimination into the CD_3 branch [to give $PhC(CH_3)=CD_2$]. Values of k_E^{H}/k_E^{D} ranging from 1·7 to 2·9 were determined by Smith and Goon.[45] If $\epsilon(X^-)$ is very small, corresponding to the usual irre-

versible *E*1 reaction, $k_{obs}^{H}/k_{obs}^{D} = k_1^{H}/k_1^{D}$. By the nature of the bonding involved ('looser' bonding for $^{\beta}$C—H in the carbonium ion than in the reactants), it can be concluded that k_1^{H}/k_1^{D} will always be greater than k_{-1}^{H}/k_{-1}^{D}, which will have a lower limit of unity. For illustrative purposes, results of a few calculations using equation (1) are presented below. The following values were used for the various isotopic ratios: $k_1^{H}/k_1^{D} = 1{\cdot}22$, $k_E^{H}/k_E^{D} = 2{\cdot}00$, $k_{-1}^{H}/k_{-1}^{D} = 1{\cdot}11$, $(X_H^-)/(X_D^-) = 1$.

$\epsilon(X^-)$	*Possible* ϵ:(X^-) *values*	k_{obs}^{H}/k_{obs}^{D}
0	Irreversible for $\epsilon = 0$	1·22
0·01	1:0·01, or 0·1:0·1, or 0·01:1, *etc.*	1·23
0·1	10:0·01, or 1:0·1, or 0·1:1, *etc.*	1·31
0·5	50:0·01, or 5:0·1, or 0·5:1, *etc.*	1·55
1	100:0·01, or 10:0·1, or 1:1, *etc.*	1·77
10	1000:0·01, or 100:0·1, or 10:1, *etc.*	2·01
100	10,000:0·01, or 1000:0·1, or 100:1, *etc.*	2·19

Under the usual reaction conditions used for isotope effect measurements, *e.g.* 0·01M-RX, it is apparent that external X^- salt would have to be added, or else ϵ would have to be quite large before an appreciable increase in k_{obs}^{H}/k_{obs}^{D} would be observed. Ion recombination is a kind of substitution reaction and, just as is the case for k_{-1}^{H}/k_{-1}^{D}, other competing substitution reactions would be expected to have small values for k_S^{H}/k_S^{D}. The net effect of such competing substitution reactions under these reversible conditions would be to use up the labelled substrate more rapidly than if it had to undergo an elimination reaction, thus increasing k_{obs}^{D}, which causes k_{obs}^{H}/k_{obs}^{D} to decrease. In the limit, only substitution takes place, and the value of k_{obs}^{H}/k_{obs}^{D} is that characteristic of the solvolytic substitution reaction alone. The k^{H}/k^{D} results of Smith and Goon[45] with different leaving groups follow this pattern:

$$PhC(CH_3)_2X \xrightarrow[50°C]{EtOH} PhC(CH_3)=CH_2 + PhC(CH_3)_2OEt$$

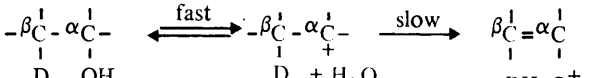
X	k_E^{H}/k_E^{D}	$k^{H}/k^{D}(D_3)$	$k^{H}/k^{D}(D_6)$	(*olefin*/*ether*)(D_0)
Chloride	2·9	1·22	1·42	0·13
p-Nitrobenzoate	2·4	1·32	1·76	1·0
Thionobenzoate	1·7	1·34	1·94	16

As far as β-hydrogen isotope effects go, reaction of the chloride, giving mostly substitution products, is a nearly normal S_N1 solvolysis reaction (the degree of ion recombination is unknown and is not necessarily very small); and reaction of the thionobenzoate is primarily a solvolytic elimination reaction, probably somewhat complicated by ion recombination. Using 1·22 for k_1^{H}/k_1^{D} and 1·11 for k_{-1}^{H}/k_{-1}^{D}, the observed 1·34 for k_{obs}^{H}/k_{obs}^{D}, and the observed 1·7 for

k_E^H/k_E^D, the value of $\epsilon(X^-)$ can be calculated from equation (1) to be 0·23, probably indicating a value of 50 or more for ϵ. It would be interesting to see if added X^- would have the predicted effect of increasing k_{obs}^H/k_{obs}^D for this case.

Although a few other measurements or estimates have been made[11,46] of the β-hydrogen isotope effect in the conversion of carbonium ions to olefins in the second step of $E1$–S_N1 solvolysis reactions, no useful correlations seem to have emerged. The technique, involving isotopic measurements on the olefinic reaction products, is straightforward and relatively simple, and this area of research merits more attention. A whole spectrum of mechanisms might be revealed, with k^H/k^D values varying through a maximum for symmetrical bonding of the abstracted proton to β-C and the solvent.

Noyce and co-workers[47] studied the primary and secondary β-hydrogen isotope effects in the acid-catalysed racemization and dehydration of 2-phenyl-2-hydroxypropionic acid and 1,2-diphenylethanol. A normal secondary β-hydrogen

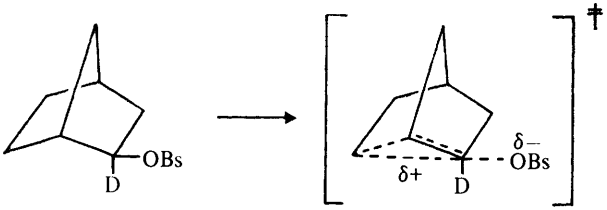


isotope effect was found for the racemization reaction, and fairly large (k^H/k^D = 1·72, 1·83) β-hydrogen isotope effects were found for the overall dehydration reactions. By an analysis similar to that used in developing equation (1) above, Noyce and co-workers concluded that the observed k^H/k^D arose from a combination of primary and secondary isotope effects, that the carbonium ion was formed rapidly and reversibly, and that the rate determining step was abstraction of the β-hydrogen by solvent.[48] It would be of interest to study the β-C carbon-14 isotope effect in a reaction such as this.

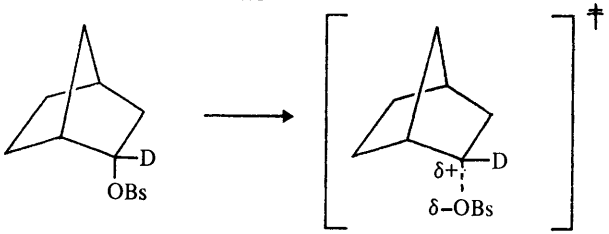
In concluding this section on β-hydrogen isotope effects in solvolytic reactions, it is of interest to review briefly the contributions made to the question of participation by the C(1)—C(6) electrons in solvolysis of norbornyl derivatives by isotope effect research. As pointed out above,[22,30,40] delocalization of a developing positive charge at α-C in an $E1$–S_N1 reaction by conjugation or neighbouring group participation reduces both the α- and β-hydrogen isotope effects. For acetolysis of *exo*- and *endo*-[2-^{2}H]norbornyl brosylates at 50 °C, Lee and Wong[30] found α-hydrogen isotope effects of $(k^H/k^D)_{exo}$ = 1·07 and $(k^H/k^D)_{endo}$ = 1·20. The isotope effect for the *endo*-compound is about normal, but that for the *exo*-compound is very low, consistent with extensive backside attack in the rate-

[46] M. S. Silver, *J. Amer. Chem. Soc.*, 1961, **83**, 3487, and references cited there.
[47] D. S. Noyce, D. R. Hartter, and R. M. Pollack, *J. Amer. Chem. Soc.*, 1968, **90**, 3791; D. S. Noyce and C. A. Lane, *ibid.*, 1962, **84**, 1641.
[48] It might be noted that this reversible carbonium ion mechanism formally bears the same relationship to the ordinary $E1$–S_N1 mechanism as the reversible and irreversible carbanion mechanisms bear to each other.

determining step. The same type conclusions were drawn from solvolysis data

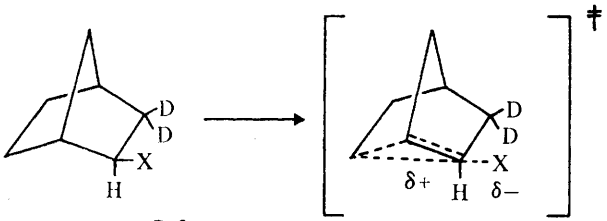


$(k^H/k^D)^{\alpha}_{exo} = 1{\cdot}07$

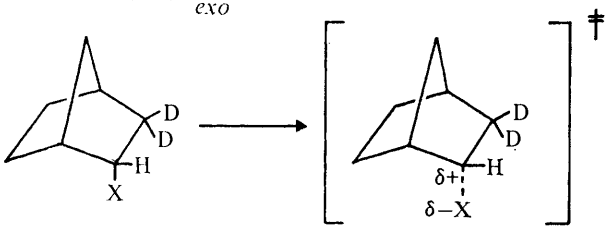


$(k^H/k^D)^{\alpha}_{endo} = 1{\cdot}20$

for β-hydrogen isotope effects for *exo*- and *endo*-[2-^{2}H]- or -[2,2-$^2H_2$]-norbornyl bromides[49] and brosylates.[50,51] Finally, and perhaps providing the strongest



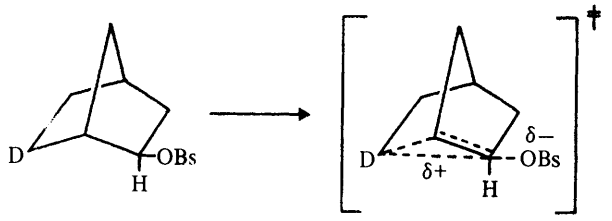
$(k^H/k^D)^{\beta}_{exo} = 1{\cdot}01 - 1{\cdot}11$



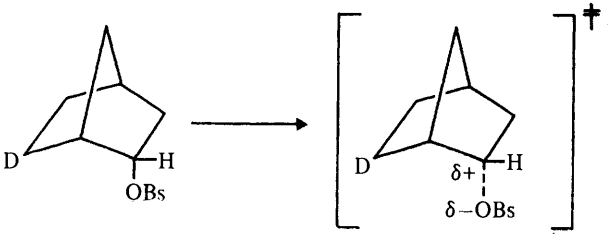
$(k^H/k^D)^{\beta}_{endo} = 1{\cdot}26 - 1{\cdot}34$

[49] J. P. Schaefer and D. S. Weinberg, *Tetrahedron Letters*, 1965, 2491; J. P. Schaefer, M. J. Dagani, and D. S. Weinberg, *J. Amer. Chem. Soc.*, 1967, **89**, 6938.
[50] J. M. Jerkunica, S. Borcic, and D. E. Sunko, *Chem. Comm.*, 1967, 1302.
[51] B. L. Murr and J. A. Conkling, *J. Amer. Chem. Soc.*, 1970, **92**, 3464.

evidence for the indicated participation, *exo*-[6-^{2}H]-norbornyl brosylates show substantial γ-hydrogen isotope effects, while *endo*-[6-^{2}H]-norbornyl brosylates show none.[52]



$$(k^H/k^D)^{\gamma}_{exo} = 1{\cdot}09 - 1{\cdot}15$$



$$(k^H/k^D)^{\gamma}_{endo} = 0{\cdot}97 - 1{\cdot}02$$

4 Isotope Effect Studies of *E*1cb Reactions[53]

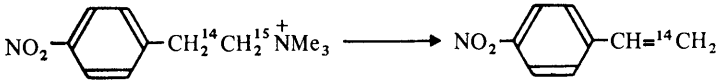
A. Labelled Y$^-$, α-C, β-C, or X.—Almost no heavy-atom isotope effect research has been carried out on reactions thought to proceed by the *E*1cb mechanism. For reactions which might have carbanion *formation* as the rate-determining step (type A, Section 2) probably the most critical test that could be applied is whether or not an isotope effect is observed if either α-C or leaving group X is labelled. The prediction is that there would be no isotope effect for either α-C or X labelled substrate for rate-determining formation of a carbanion, whereas there would be isotope effects for either the *E*2 or reversibly formed carbanion (type B, Section 2) mechanism. The only four α-C carbon-14 labelled cases examined,[12,54] decomposition of ethyl-, n-propyl-, t-butyl-, and 2-(*p*-nitro-

[52] J. M. Jerkunica, S. Borcic, and D. E. Sunko, *J. Amer. Chem. Soc.*, 1967, **89**, 1732; B. L. Murr, A. Nickon, T. D. Swartz, and N. H. Werstiuk, *ibid.*, 1967, **89**, 1730, and earlier papers cited there.

[53] An excellent critical review of the carbanion mechanism for olefin-forming eliminations appeared recently, D. J. McLennan, *Quart. Rev.*, 1967, **21**, 490.

[54] E. M. Hodnett and W. J. Dunn, tert., *J. Org. Chem.*, 1967, **32**, 4116.

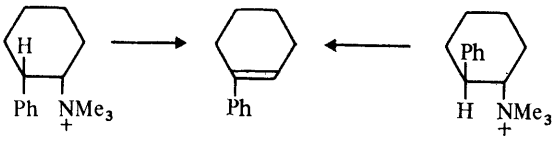
phenyl)-ethyltrimethylammonium salts, have all shown sizeable isotope effects (k^{12}/k^{14} = 1·026—1·075). A nitrogen isotope effect, k^{14}/k^{15} = 1·024 at 98 °C, was also observed[55] with the latter compound. Clearly, rate-determining carbanion formation cannot be the elimination reaction mechanism in these cases. Furthermore, the β-hydrogens of 2-*p*-(nitrophenyl)ethyltrimethylammonium iodide did not undergo exchange when heated with tritiated water at 100 °C for one elimination reaction half-life,[56] so the reversible *E*1cb mechanism is also inconsistent with the experimental results. It appears that all the above-mentioned compounds react by the *E*2 mechanism (see the next section).



^{14}C: k^{12}/k^{14} = 1·078; ^{15}N: k^{14}/k^{15} = 1·024; no α β–H exchange with HTO

Mechanism: *E*2, not *E*1cb

Although a few more leaving-group (X), nitrogen, and sulphur isotope-effects have been measured (see the *E*2 Section below) only one other case is of interest in searching for the *E*2–*E*1cb mechanistic border. For the decomposition of *cis*-2-phenylcyclohexyltrimethylammonium iodide, which is thought to undergo an *E*2 *anti* elimination, a normal nitrogen isotope effect, k^{14}/k^{15} = 1·012, was found by Ayrey, Buncel, and Bourns.[57] For the isomeric *trans*-compound, which can react to give the conjugated olefin only by a *syn*-elimination (related deuterium tracer research had ruled out an ylide mechanism), a very small nitrogen isotope effect, k^{14}/k^{15} = 1·002, was measured.[57] The β-deuterium labelled compound did not exchange with solvent hydrogen under elimination reaction



^{15}N: k^{14}/k^{15} = 1·012

anti-*E*2

^{15}N: k^{14}/k^{15} = 1·002

syn-*E*2 or *E*1cb

conditions, so the reversible carbanion mechanism is ruled out. If the small nitrogen isotope effect is real (error limits were not specified), its very existence rules out an *E*1cb mechanism involving rate-determining carbanion formation; but if this is an *E*2 reaction, it must certainly lie near the *E*1cb border. It would

[55] E. M. Hodnett and J. J. Sparapany, *Pure Appl. Chem.*, 1964, **8**, 385.
[56] E. M. Hodnett and J. J. Flynn, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 2300.
[57] G. Ayrey, E. Buncel, and A. N. Bourns, *Proc. Chem. Soc.*, 1961, **458**.

be interesting to have comparative β-deuterium and α-carbon-14 isotope-effect data on these two isomeric compounds.

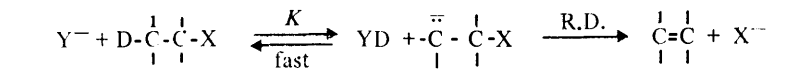
No isotope effect measurements have been made for compounds thought to react by either of the *E*1cb mechanisms using reactants labelled at β-C, but since all bimolecular elimination mechanisms would be predicted to show β-C isotope effects, no qualitative mechanistic distinction is possible. The magnitudes of such effects would, however, be useful in placing the mechanism of a given reaction at a certain position within the *E*2 mechanistic spectrum, a matter which will be dealt with more fully in the next section.

For a reactant labelled at incoming nucleophile Y, a primary kinetic isotope effect (perhaps low because bond formation is involved) should be observed for reaction by the *E*2 or the type A *E*1cb mechanism, whereas for the type B *E*1cb mechanism only an equilibrium (probably very low and capable of independent calibration) isotope effect would be expected. No such experiment has been carried out, but it merits serious consideration.

B. Labelled β-Hydrogen.—The presence of isotopic exchange between the β-hydrogens of an elimination reaction substrate and the deuterium (or tritium) labelled solvent/base system (or *vice versa*) serves to identify reversible carbanion formation. It is usually considered that this identification of a carbanion in such a system indicates the existence of an *E*1cb rather than an *E*2 reaction mechanism. However, this does not necessarily follow, since, as was pointed out by Hine, Wiesboeck, and Ramsay[58] in 1961, and later more clearly by Breslow,[59] the elimination reaction mechanism might be *E*2 with carbanion formation being simply an irrelevant side reaction. This possibility has been widely discounted[8,53,58,60] on various grounds, but remains a viable criticism. As pointed out above, heavy-atom isotope effect research might possibly settle this question.

Evidence on this point may also be obtained from β-hydrogen isotope effect studies. For both the *E*2 and type A *E*1cb mechanisms, primary β-hydrogen isotope effects are to be expected, so no qualitative mechanistic distinction is possible. Given sufficient calibration data, some mechanistic use might be made of relative magnitudes of isotope effects. For type B *E*1cb reactions, the situation is rather complex, but has mechanistic promise. For the frequently encountered case where Y^- is the conjugate base of the solvent and both labelled and unlabelled substrates are allowed to react in the presence of excess unlabelled solvent, no useful isotope effect data can be obtained, since the labelled substrate quickly loses its label, and thus will show no isotope effect in the elimination reaction, regardless of the mechanism. For cases where an aprotic solvent is used, and the labelled and unlabelled substrates are separately allowed to react with Y^-, the carbanion from each isotopic isomer can only return to its own isotopic precursor. The *E*2 and type A *E*1cb mechanisms will thus proceed with their characteristic normal primary isotope effects, whereas the type B *E*1cb

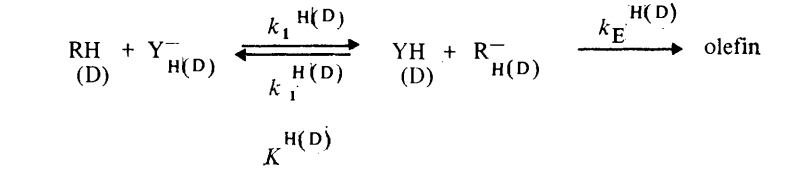
[58] J. Hine, R. Wiesboeck, and O. B. Ramsay, *J. Amer. Chem. Soc.*, 1961, **83**, 1222.
[59] R. Breslow, *Tetrahedron Letters*, 1964, 399.
[60] H. M. R. Hoffmann, *Tetrahedron Letters*, 1967 4393.



mechanism will show only a small equilibrium isotope effect, reflecting the different equilibrium concentrations of the carbanion.

By comparing the rate of reaction of the unlabelled substrate in the unlabelled protic solvent to that of the labelled substrate in the labelled protic solvent, an equivalent analysis is possible. A normal primary isotope effect will be obtained if reaction takes place by the *E*2 or type A *E*1cb mechanism, whereas an equilibrium (solvent) isotope effect will be obtained if the reaction mechanism is type B *E*1cb.

A general formulation of the *E*1cb mechanisms for such a case may be developed using the usual steady-state treatment:



The rate of olefin formation for the unlabelled compound in the unlabelled solvent will be:

$$\text{rate}_H = k_E{}^H[R_H^-] = \frac{k_E{}^H k_1{}^H[RH][Y^-]}{k_E{}^H + k_{-1}{}^H[YH]}$$

Utilizing a similar expression for reaction of the labelled compound in the labelled solvent, and recognizing that R^- is the same carbanion whether generated from RH or RD so that $k_E{}^H = k_E{}^D$, and defining $\delta = k_{-1}{}^H[YH]/k_E{}^H$, general equation (2) is obtained:

$$\frac{\text{rate}_H}{\text{rate}_D} = \frac{k_1^H}{k_1^D}\,\frac{[RH]}{[RD]}\,\frac{[Y_H^-]}{[Y_D^-]}\left[\frac{1 + \delta k_{-1}^D\,[YD]/k_{-1}^H\,[YH]}{1 + \delta}\right] \qquad (2)$$

For an *E*1cb reaction involving rapid and reversible carbanion formation (type B), $\delta \gg 1$, the overall rate will usually be second-order, first-order each in RH and Y_H^- (or RD and Y_D^-), so that

$$\frac{k_{obs}{}^H}{k_{obs}{}^D} = \frac{k_1{}^H k_{-1}{}^D[YD]}{k_1{}^D k_{-1}{}^H[YH]} = \frac{K^H[YD]}{K^D[YH]}$$

If, as is frequently the case, YH and YD are solvent, then their concentrations are effectively constant and equal and $k_{obs}{}^H/k_{obs}{}^D = K^H/K^D$, the ratio of the isotopic equilibrium constants. Depending on the strength of bonding in RH *vs.*

BH this ratio may range from somewhat smaller (the usual case) to somewhat larger than unity.

In Skell and Hauser's first investigation[61] of possible exchange of β-hydrogens under elimination reaction conditions, 2-phenylethyl bromide did not accumulate deuterium from the labelled basic aqueous-alcoholic solvent. The type B *E*1cb (reversible carbanion formation) mechanism was thus ruled out. Since that time, many investigations with similar results have been carried out.[62] Several cases[63] are now known where exchange does take place in such experiments and, for some of these, isotope effects have been determined as well.

Isotope effects on exchange reactions themselves were found to range from very high,[64] $k_1^H/k_1^D \sim 12$ for toluene and ethylbenzene, to very low, $k_1^H/k_1^D = 0{\cdot}5$—$1{\cdot}5$ for 2-octyl phenyl sulphone,[65] $1{\cdot}3$—$1{\cdot}4$ for 2,2-dihalogeno-1,1,1-trifluoroethanes,[66] and $1{\cdot}76$ for *cis*-2-methoxycyclohexyl *p*-tolyl sulphone.[67] The low values of k_1^H/k_1^D were attributed[65] to rapid internal return to R^- of the particular H (or D) originally abstracted by Y^-, so that the real rate process is one of diffusion exchange of YH and YD. Alternatively, the low values might arise from either very slight or very extensive transfer of H from R to Y at the activated complex.[31] A plot[68] of log k^H/k^D *vs.* the difference in acid dissociation constants for a wide variety of YH and RH cases goes through a maximum as might be expected.[31] In recent interesting research,[69] triptycene showed a normal isotope effect in the exchange reaction, $k_1^D/k_1^T = 2{\cdot}24$ (equivalent to $k_1^H/k_1^D \cong 6{\cdot}16$) showing the stability of a bridgehead carbanion.

For the *E*1cb type B elimination of 4-methoxy-2-butanone to 3-buten-2-one and of 4-methoxy-4-methyl-2-pentanone to 4-methyl-3-penten-2-one,[70] exchange of the β-hydrogens (those α to the carbonyl group) with D_2O–OD^- was fast, and the overall isotope effects were $0{\cdot}87$ and $0{\cdot}77$ (k_{obs}^H/k_{obs}^D in the above equation). Similarly, Crosby and Stirling[71] observed rapid exchange and $k_{obs}^H/k_{obs}^D = 0{\cdot}66$ and $0{\cdot}78$ for the elimination of phenoxide from 2-phenoxy-

[61] P. S. Skell and C. R. Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1661.
[62] A partial list of such studies includes W. H. Saunders, jun., and M. R. Schreiber, *Chem. Comm.*, 1966, 145; V. J. Shiner, jun., and M. L. Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 4095; P. J. Smith and A. N. Bourns, *Canad. J. Chem.*, 1970, **48**, 125; J. L. Coke, M. P. Cooke, jun., and M. C. Mourning, *Tetrahedron Letters*, 1968, 2247; J. L. Coke and M. P. Cooke, jun., *ibid.*, 1968, 2253; J. L. Coke and M. C. Mourning, *J. Amer. Chem. Soc.*, 1968, **90**, 5561; J. L. Coke and M. P. Cooke, jun., *ibid.*, 1967, **89**, 6701; N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *ibid.*, 1963, **85**, 3199; J. Weinstock, J. L. Bernardi, and R. G. Pearson, *ibid.*, 1958, **80**, 4961; T. I. Crowell, R. T. Kemp, R. E. Lutz, and A. A. Wall, *ibid.*, 1968, **90**, 4638; J. Hine and P. B. Langford, *J. Org. Chem.*, 1962, **27**, 4149; and ref. 56.
[63] F. G. Bordwell, M. M. Vestling, and K. C. Yee, *J. Amer. Chem. Soc.*, 1970, **92**, 5950; see also refs. 58 and 59 for earlier examples.
[64] A. Streitwieser, jun., W. C. Langworthy, and D. E. Van Sickle, *J. Amer. Chem. Soc.*, 1962, **84**, 251.
[65] D. J. Cram, D. A. Scott, and W. D. Nielson, *J. Amer. Chem. Soc.*, 1961, **83**, 3696.
[66] J. Hine, R. Wiesboeck, and R. G. Ghirardelli, *J. Amer. Chem. Soc.*, 1961, **83**, 1219.
[67] J. Hine and O. B. Ramsay, *J. Amer. Chem. Soc.*, 1962, **84**, 973.
[68] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc.*, 1966, **294**, 273.
[69] A. Streitwieser, jun., and G. R. Ziegler, *J. Amer. Chem. Soc.*, 1969, **91**, 5081.
[70] L. R. Fedor, *J. Amer. Chem. Soc.*, 1969, **91**, 908.
[71] J. Crosby and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1970, 679.

ethyldimethylsulphonium iodide and 2-phenoxyethyl methyl sulphone, in full agreement with the *E*1cb type B mechanism. Such inverse isotope effects could

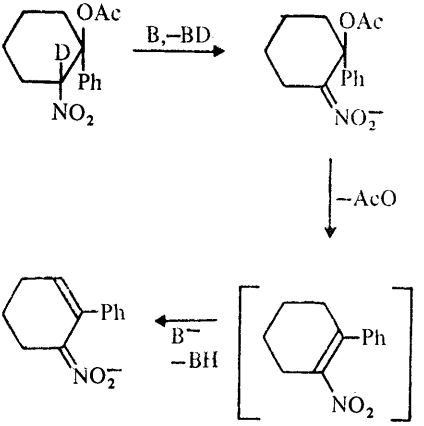
$$PhSO_2^{\beta}CH_2^{\alpha}CH_2OPh \underset{D_2O}{\overset{OD^-}{\rightleftharpoons}} PhSO_2\bar{C}DCH_2OPh \xrightarrow{-OPh} PhSO_2CD{=}CH_2$$

also be possible for reaction by an *E*2 mechanism if the primary isotope effects were small (unsymmetrical transfer[31] of H from β-C to Y) and the H_2O–OH^- *vs.* D_2O–OD^- isotope effects on *E*2 reactions were less than unity. Steffa and Thornton[72] studied such solvent–base isotope effects for the *E*2 reactions of a series of β-phenethyl derivatives, and found k^H/k^D values of 0·56—0·63 at 80·45 °C. It seems likely that the above reactions are in fact *E*1cb and not *E*2. Additional evidence on this point, which also bears on the details of the slow phenoxide elimination step is provided by Redman and Stirling.[73] Substitution of phenyl for one of the hydrogens on α-C has very small effect (a factor of 1·3) on the overall rate of the reaction, whereas a similar substitution for a typical *E*2 reaction, dehydrobromination of ethyl bromide, increases the rate by a factor of 50. Thus, the activated complex for elimination from the sulphone must have very little double bond character (either *E*2 or the second step of *E*1cb), and also very little $^{\alpha}$C—X bond rupture. Isotope effect studies with α-C carbon-14 labelled sulphones having various *p*-substituted phenyl groups at α-C should reveal very nicely any trends in the double bond character of the activated complex. Use of thiophenoxy instead of phenoxy sulphones increases the double bond character of the elimination reactions,[73] and comparative α-C carbon-14 isotope-effect studies could go a long way in calibrating the degree of double bond character in activated complexes of various mechanisms. This reaction might also serve as a useful vehicle for the study of secondary hydrogen isotope effects in *E*1cb reactions. Would the overall rate of the reaction be affected by substituting deuterium for hydrogen at α-C? This would correspond to a β-hydrogen isotope effect in solvolytic reactions, and has been very little studied. Streitwieser and Van Sickle[74] have measured secondary α- and β-hydrogen isotope effects in hydrogen exchange reactions of ethylbenzene.

Referring again to equation (2), for an *E*1cb reaction with rate-determining carbanion formation (type A), $\delta \ll 1$, the overall rate will be first-order each in RH and Y_H^- (or RD and Y_D^-), so $k_{obs}{}^H/k_{obs}{}^D = k_1{}^H/k_1{}^D$. This is the same kinetic expression as for the *E*2 reaction and variable k^H/k^D ratios would be expected in both cases, depending on the degree of hydrogen transfer between Y^- and β-C at the activated complex, a maximum being observed for the symmetrical case.[31] As mentioned above, isotope effect studies with α-C or X labelled compounds would provide a critical test for distinguishing between the *E*2 and *E*1cb type A mechanisms.

[72] L. J. Steffa and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 6149.
[73] R. P. Redman and C. J. M. Stirling, *Chem. Comm.*, 1970, 633.
[74] A. Streitwieser, jun., and D. E. Van Sickle, *J. Amer. Chem. Soc.*, 1962, **84**, 254.

Bordwell and co-workers[63,75] have presented persuasive arguments that an *E*1cb type A mechanism is followed in the elimination of acetic acid from 2-phenyl-2-acetoxy-1-nitrocyclohexanes and cyclopentanes and of methanol from 2-phenyl-*trans*-2-methoxynitrocyclopentane. Large (k_{obs}^{H}/k_{obs}^{D} = 4·9—8·1) β-deuterium isotope effects are observed in all of the reactions, as would be expected for the *E*1cb type A mechanism for more or less symmetrical transfer of the β-hydrogen from β-C to X^-. A reaction such as this might be very useful



B	k_{obs}^{H}/k_{obs}^{D}
MeO⁻/MeOH	8.0
piperidine	4.9

in investigating the possibility of changing the relative $^{\beta}$C—H *vs.* Y—H bonding in the activated complex (and thus the magnitude of k_{obs}^{H}/k_{obs}^{D}) by changing the strength of the base used to abstract the β-deuterium. If the change in k_{obs}^{H}/k_{obs}^{D} of 8·0 to 4·9 when the base is changed from methoxide ion to piperidine is caused by a difference of this type, a more extensive investigation of other bases would appear to have merit. It would also be of interest to investigate the possibility of a secondary isotope effect for a compound such as this labelled with deuterium at the 6-position.

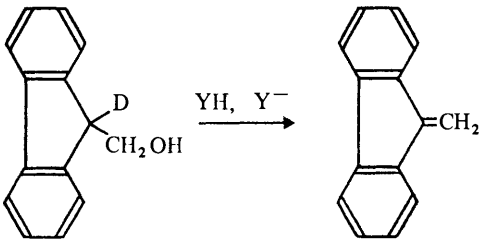
In what is suggested to be another carbanion elimination reaction of type A (no exchange could be detected) Cram and Wingrove found a low β-deuterium isotope effect of k_{obs}^{H}/k_{obs}^{D} = 1·2 in the reaction of 2-methyl-3-phenyl-1,1,1-trifluoropropane with potassium t-butoxide in t-butyl alcohol.[76] A check for an isotope effect with the α-C or X labelled material would be of interest to see if this might be an *E*2 reaction.

Another variant of the *E*1cb mechanism has been suggested by Rappoport

[75] F. G. Bordwell, R. L. Arnold, and J. B. Biranowski, *J. Org. Chem.*, 1963, **28**, 2496.
[76] D. J. Cram and A. S. Wingrove, *J. Amer. Chem. Soc.*, 1964, **86**, 5490.

and co-workers[77] and supported by Bordwell's group.[78] If effectively all the substrate is converted by the base to the carbanion in a rapid reaction, additional base will not increase the concentration of the carbanion further, and the reaction will become pseudo-first-order. As defined, β-hydrogen isotopic isomers would both be converted completely to carbanion, and there would be no isotope effect since the isotopically substituted atom is no longer in the molecule in the following rate-determining step. In such a reaction Rappoport and Schohamy[77] found $k^H/k^D = 0{\cdot}93$ for the elimination of HCN from 2,6-dimethyl-4-(1,1,2,2-tetracyanoethyl)aniline in the presence of triethyl- or tri-n-butyl-amine. Bordwell, Yee, and Knipe[78] found $k^H/k^D = 1{\cdot}7$ for the overall elimination of methanol from 2-phenyl-*trans*-2-methoxy-1-nitrocyclopentane using sodium methoxide in methanol. The value of k^H/k^D for the first step (carbanion formation) was a normal 7·5, the same as that observed[63] for carbanion formation from 1-phenyl-2-nitropropane using potassium t-butoxide in t-butyl alcohol.

More O'Ferrall and Slae[79] have carried out an extensive isotope effect study of a reaction thought to occupy the *E*1cb–*E*2 mechanistic border. The β-elimination of water from 9-fluorenylmethanol to form dibenzofulvene was investigated in water, methanol, t-butyl alcohol, and mixtures of the latter two alcohols in the presence of the respective solvent conjugate bases. This substrate is characterized by a very poor leaving group, OH, and a β-hydrogen which is very acidic by virtue of the aromatic nature of the carbanion formed by its loss. Both factors favour an *E*1cb mechanism, and for all solvent systems the primary mechanism appears to be *E*1cb, with carbanion formation being rate-determining in t-butyl alcohol (type A mechanism) and carbanion decomposition being rate-determining in the other solvents (type B mechanism). Various amounts of simultaneous competitive reaction by an *E*2 mechanism are also proposed.



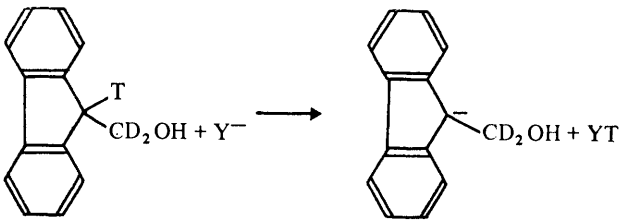
In water and methanol, exchange was rapid compared to elimination. In agreement with most of the work mentioned above, the exchange reaction isotope effects were large, with $k^H/k^D \cong 7$. For solvent water, the overall

[77] Z. Rappoport, *Tetrahedron Letters*, 1968, 3601; Z. Rappoport and E. Shohany, *Israel J. Chem. Proc.*, 1968, **6**, 15.
[78] F. G. Bordwell, K. C. Yee, and A. C. Knipe, *J. Amer. Chem. Soc.*, 1970, **92**, 5945.
[79] R. A. More O'Ferrall and S. Slae, *J. Chem. Soc.* (*B*), 1970, 260; R. A. More O'Ferrall, *ibid.*, 1970, 268.

(solvent) isotope effect was $k^H/k^D = 0{\cdot}92$ (comparing the rate of the unlabelled compound in unlabelled water with the rate of the labelled compound in labelled water). The corresponding value for solvent methanol was 0·36. These are reasonable values for solvent isotope effects on the substrate–carbanion equilibria in type B *E*1cb reactions. Again, it is unlikely that a combination of a primary and solvent isotope effect on an *E*2 mechanism could give such low overall values for k^H/k^D. However, on the basis of detailed analyses of the initial rates of reaction of the labelled substrate in unlabelled solvent and of the unlabelled substrate in labelled solvent, the authors concluded[79] that a small fraction of the reaction proceeds by a competitive *E*2 mechanism.

In pure t-butyl alcohol or in its mixtures with 1·6 or 1·84% methanol the overall rate of the reaction became much greater and no exchange was detected. The overall isotope effect in the pure t-butyl alcohol was large, $k^H/k^D = 7{\cdot}5$, but when 1—2% methanol was added it dropped to *ca.* 3·3 (with still no exchange). More O'Ferrall's favoured interpretation[79] of these results is that the rate-determining step of the elimination reaction in pure t-butyl alcohol is carbanion formation (*E*1cb type A mechanism), and that addition of small amounts of methanol results in the incursion of a slower competitive reaction by an *E*2 mechanism which has a small value for k^H/k^D. When more methanol is added, carbanion formation becomes reversible (*E*1cb type B mechanism) and k^H/k^D falls to less than unity. Presumably the competitive *E*2 reaction retains some, but not major, importance. The alternative interpretation that the elimination reactions observed in some or all of these solvent–base systems are due to *E*2 reactions with different isotope effects owing to different degrees of transfer of H from β-C to the base, could be investigated by looking for isotope effects with α-C or X labelled compounds. Such studies would be especially valuable in comparing the results in pure t-butyl alcohol with those in t-butyl alcohol with 1—2% of methanol added. It would also be of interest to investigate more thoroughly the β-hydrogen isotope effects in t-butyl alcohol containing slightly more than 2% methanol where δ values in equation (2) might be expected to be neither very large nor very small, leading to intermediate values for k^H/k^D.

C. Labelled α-Hydrogen.—The above studies of More O'Farrell and Slae[79] provide the only definitive data available on α-hydrogen isotope effects in *E*1cb elimination reactions. β-Tritium exchange was measured for the αα-$^2H_2$,β-^{3}H and αα-H_2,β-^{3}H compounds in water, $k^H/k^D = 1{\cdot}02$, and in methanol, $k^H/k^D = 1{\cdot}10$:



The corresponding value found by Streitwieser and Van Sickle[74] in the formation of the carbanion from ethylbenzene in the presence of lithium cyclohexylamide was $k^H/k^D = 1{\cdot}11$. These α-effects correspond to β-effects in solvolytic reactions, but the cause of the effects is not as well understood. More O'Ferrall suggests that the difference between water and methanol may reflect an important contribution from carbon–oxygen bond breaking in the *E*1cb transition state (presumably in the elimination step). It would be interesting to compare the above results with the corresponding one for reaction in pure t-butyl alcohol where, supposedly, carbanion formation is rate-determining. There may be unrealised potential for *E*1cb–*E*2 borderline mechanistic discrimination in the use of α-hydrogen isotope effects.

5 Isotope Effect Studies of *E*2 Reactions

A. Introduction—A General Reaction Scheme.—Of all the ways of representing the variety of activated complexes for the *E*2 spectrum of mechanisms, that suggested by More O'Ferrall[80] seems to this author to be the most useful generally. It is well suited to discussions of variations of isotope effects with structures in elimination reaction systems. Figure 1 is a schematic representation

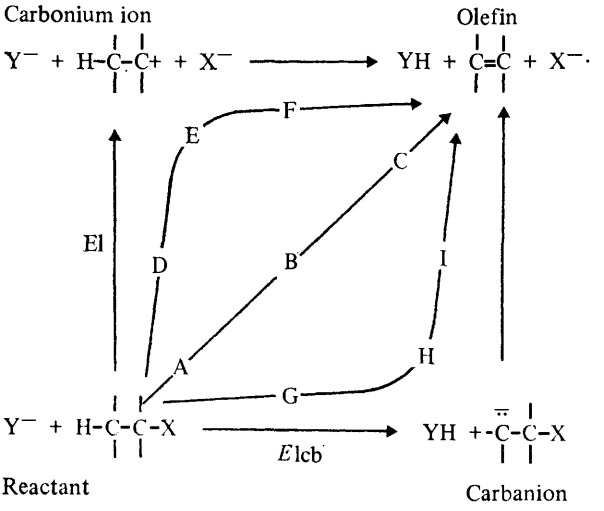


Figure 1 *E2 mechanistic spectrum*

of various *E*2 mechanisms, adapted from the potential surface diagrams of More

[80] R. A. More O'Ferrall, *J. Chem. Soc.* (*B*), 1970, 274.

O'Ferrall.[81] Each letter (actually, each spot) within the diagram represents a different activated complex, each with its own separate potential surface, and the positions of the letters relative to the species at the corners of the diagram indicate the structural relationships of the various activated complexes and their positions along the reaction co-ordinate. Thus, activated complex A would be described as 'reactant like,' with only slight weakening of the $^{\beta}$C—H and $^{\alpha}$C—X bonds and with only slight $^{\beta}$C—$^{\alpha}$C double bond character. This activated complex, in accordance with the Hammond postulate,[82] would be for a reaction giving a very stable olefin. Activated complex F would be described as 'carbonium-ion like' *and* 'olefin like', with very weak $^{\alpha}$C—X bonding, much $^{\beta}$C—$^{\alpha}$C double bond character, and extensive transfer of H from β-C to X^-. It is a relatively simple matter to make qualitative predictions of isotope effects for the various possible labelled molecules from the strengths of the various bonds as analysed above. The procedure also lends itself to quantitative isotope effect calculations of the type mentioned in the Introduction. For instance, in a qualitative sense, for activated complex F, a large isotope effect would be predicted for the X labelled compound and a small isotope effect (on the Y—H side of the maximum) would be predicted for the β-hydrogen labelled compound. It is also easy to see how substrate structural changes will affect the position and bonding of the activated complex and, hence, how the isotope effects will change with structural changes. For instance, if the elimination of β-phenethyl chloride had a 'central' activated complex represented by B, substitution of a nitro-group in the *para* position of the ring would make the reaction more 'carbanion like', and the new activated complex would shift toward H with an accompanying increase in transfer of H from β-C to Y giving a smaller β-hydrogen isotope effect (assuming a near symmetrical case for the unsubstituted compound), a decrease in the $^{\beta}$C—$^{\alpha}$C double bond character, and an increase in the $^{\alpha}$C—X bond strength, giving a smaller isotope effect for the X labelled compound. It is to be noted that this change from F to H results in the activated complex becoming *more* 'carbanion like' as the structural change results in greater carbanion stability. This is opposite to the Hammond postulate prediction because the effect of the structural change is applied in a fashion perpendicular rather than parallel to the primary reaction co-ordinate. This appears to be a general phenomenon, and is discussed in considerable detail by More O'Ferrall,[80] following the earlier work of Thornton and co-workers.[72,83]

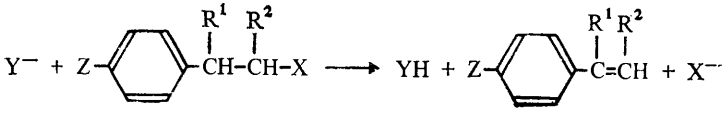
B. Isotope Effects in the β-Phenethyl System.—The β-phenethyl system (10) seems ideally suited to the application of isotope effect studies in identifying

[81] In More O'Ferrall's procedure, a potential surface is constructed with the reactant, product, carbanion, and carbonium ion occuping potential wells at the four corners of a square. Potential energy contour lines are drawn in the usual fashion to show saddle points (activated complexes) between various pairs of species at the four corners of the diagram, *etc.* The position of the reaction co-ordinate and the activated complex for a given reaction will depend on the relationship of the structure of the activated complex to the structures and energies of the four species at the corners of the potential surface.

[82] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

[83] E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 2915.

changes in the nature of activated complexes caused by changes in substrate structure or the reaction medium. Changes in X, Y^-, Z, R^1 and R^2 can be



(10)

expected to shift the activated complex in all directions from that for a reference 'central' mechanism represented by B in Figure 1. No systematic study of this type has been carried out, but most of the scattered data available seem to be consistent with analyses of the types mentioned in the introduction to this section. For instance, in the decomposition of ethyltrimethylammonium iodide in ethanol–ethoxide ion at 60 °C, the nitrogen isotope effect k^{14}/k^{15} is 1·0173[84] and the β-deuterium isotope effect k^H/k^D is ~6 (estimated from higher temperature data[85]). For β-phenethyltrimethylammonium bromide, the corresponding values are k^{14}/k^{15} = 1·0094[84] and k^H/k^D ~ 3.[86] If ethyltrimethylammonium ion is taken to have an activated complex near B in Figure 1 with the β-hydrogen about equally bonded to β-C and Y, replacement of a β-hydrogen by phenyl would make the remaining β-hydrogens more acidic, shifting the activated complex toward H. This would give a more carbanion-like activated complex, with greater transfer of H from β-C to Y, with an accompanying reduction in the β-hydrogen isotope effect. There should also be less weakening of the $^{\alpha}$C—N bond, with an accompanying reduction in the nitrogen isotope effect. These are exactly the results observed.

Another similar example is provided by Saunders and Edison's[86] β-deuterium isotope effect data for different leaving groups. For (10; Z = R^1 = R^2 = H), with X = Br, OTs, $\overset{+}{S}Me_2$, and $\overset{+}{N}Me_3$, k^H/k^D = 7·11, 5·66, 5·07, and 2·98. The order given would correspond to increasing carbanion character in the activated complex, and would be represented by a shift from near B toward H in Figure 1. These changes should be accompanied by increasing transfer of H from β-C to H, and thus by decreasing β-deuterium isotope effects, as observed. Consistent with this, Saunders, Bushman, and Cockerill[87] concluded that there was *less* carbanion character in the activated complex for the decomposition of β-phenethyltrimethylammonium bromide in t-butyl alcohol–t-butoxide than in ethanol–ethoxide, on the basis of higher β-deuterium isotope effects[86,87] and lower Hammet ρ values in the former solvent system.

It is surprising that no one seems to have measured β-deuterium isotope effects in (10) with R^1, R^2, and X constant and Z varying, say from CH_3O to

[84] G. Ayrey, A. N. Bourns, and V. A. Vyas, *Canad. J. Chem.*, 1963, **41**, 1759.
[85] V. J. Shiner, jun., and M. L. Smith, *J. Amer. Chem. Soc.*, 1958, **80**, 4095.
[86] W. H. Saunders, jun., and D. H. Edison, *J. Amer. Chem. Soc.*, 1960, **82**, 138.
[87] W. H. Saunders, jun., D. G. Bushman, and A. F. Cockerill, *J. Amer. Chem. Soc.*, 1968, **90**, 1775.

CH_3 to H to Cl to NO_2. Hammett ρ values for such reactions all seem to be positive,[88] so it is quite likely that the activated complexes will all lie on the carbanion side (the 'H side of B') in Figure 1. Thus, for the substituent series suggested, the β-deuterium isotope effects should decrease regularly (or perhaps increase to a maximum and then decrease). By changing R^2 in (10) to methyl or phenyl, the whole series should be transferred toward the carbanion side of Figure 1, so that the expected maximum in the β-deuterium isotope effect could surely be found.

The α-deuterium isotope effect data of Cockerill[89] support the argument that electron-withdrawing substituents on the ring in these systems shift the mechanism away from the carbonium ion or olefin-like area toward the carbanion side of Figure 1. He found α-deuterium isotope effects of k^H/k^D = 1·047, 1·043, and 1·017 in (10; $R^1 = R^2$ = H, X = OTs) for Z = CH_2O, H, and Cl, respectively, indicating decreasing sp^2 character for α-C in the order listed. McFarlane[90] found low, k^H/k^D = 2·3—2·8, β-deuterium isotope effects for such toluene-*p*-sulphonates, and interpreted his results in terms of a carbonium-ion-like *E*2 reaction, with the β-hydrogen less than half transferred from β-C to Y^-. If such is the case, large and decreasing isotope effects would be expected for X labelled compounds as the substituent Z becomes more electron withdrawing. Such experiments have not yet been carried out. However, in closely related work, the nitrogen isotope effects measured by Bourns and Smith[91] for Z = CH_3O, H, and Cl in (10; $R^1 = R^2$ = H, X = $\overset{+}{N}Me_3$) were k^{14}/k^{15} = 1·014, 1·015, and 1·011, respectively. This again would correspond to more carbanion character for the activated complex of the chloro-compound, with an accompanying decreased weakening of the $^{\alpha}$C—N bond and a lower isotope effect.

Especially interesting studies of changing isotope effects with changing reacton media have been reported by Saunders, Cockerill, and co-workers[92] in their work with β-phenethyldimethylsulphonium salts, (10; Z = $R^1 = R^2$ = H, Xi = $\overset{+}{S}Me_2$). In the reaction of hydroxide ion with the sulphonium bromide in water–dimethyl sulphoxide mixtures the rate increased sharply with increasing DMSO content and the sulphur isotope effect decreased from k^{32}/k^{34} = 1·0074 in pure water to 1·0011 in ~20% DMSO. The β-deuterium isotope effect did not change very much in this solvent range, but when the DMSO content was increased further, k^H/k^D increased to a maximum and then decreased again. The effect of adding DMSO was interpreted in terms of an increase in the effective base strength of hydroxide ion due to solvation changes, thus shifting the activated complex toward the carbanion-like side of the *E*2 spectrum (from near B toward H or G in Figure 1). This should result in decreased weakening

[88] C. H. DePuy and C. A. Bishop, *J. Amer. Chem. Soc.*, 1960, **82**, 2532, and earlier research cited there.
[89] A. F. Cockerill, *Tetrahedron Letters*, 1969, 4913; see also ref. 26 for other α-deuterium isotope effects in the β-phenylethyl system.
[90] F. E. McFarlane, *Diss. Abs.* (*B*), 1969, 2358.
[91] A. N. Bourns and P. J. Smith, *Proc. Chem. Soc.*, 1964, 366.
[92] A. F. Cockerill, *J. Chem. Soc.* (*B*), 1967, 964; A. F. Cockerill and W. H. Saunders, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 4985, and earlier papers in the series cited there.

of the $^{\alpha}$C—S bond, giving decreased sulphur isotope effects, as observed. As the DMSO content is increased even further, the carbanion becomes even more stable and, now in accordance with the Hammond postulate,[82] the activated complex becomes increasingly more reactant-like (corresponding to a shift from the G–H area toward A in Figure 1). Assuming that the transfer of H from β-C to Y was *more* than half complete at the saddle point in the 20% DMSO solution, adding DMSO and making the activated complex more reactant-like should result first in having H symmetrically bonded to Y and β-C (maximum k^{H}/k^{D}), and then to having H *less* than half transferred from β-C to Y (decreasing k^{H}/k^{D}) as observed. Thus, as the DSMO content is increased, the *E*2 saddle points on the potential surfaces represented in Figure 1 would move from somewhere near B toward the area between G and H, and then back toward A.

The only labelled carbon isotope effect studies in β-phenethyl systems were carried out on *p*-nitrophenethyltrimethylammonium salts (10; Z = NO_2, R^1 = R^2 = H, X = $\overset{+}{N}Me_3$), and in that case widely divergent values were reported for the same effect from two different laboratories. For the α-C labelled compound, Hodnett and Dunn[54] found k^{12}/k^{14} = 1·078, whereas Simon and Mullhofer's value for the same effect was 1·026. The reason for the discrepancy is not known and, in any event, comparative data for related compounds are needed before useful mechanistic conclusions can be drawn. β-Tritium[12,55,56] and amino-nitrogen[55] isotope effects were also reported for this compound, but again lack of comparative data precludes mechanistic speculation, except for the very important point that these studies confirm that the mechanism is *E*2, and not *E*1cb.

Other β-deuterium isotope-effect studies of *E*2 reactions which seem to have substantial carbanion character are those of England and McLennan on DDT,[93] Yano and Oae on β-phenylsulphonylethyl toluene-*p*-sulphonate,[94] and Baker and Spillett on β-phenethyl methyl sulphoxide.[95] A particularly interesting and readable account of the use of tracer and isotope-effect data in eliminating all other mechanisms than *E*2 for the bimolecular elimination reaction of β-phenethyltrimethylammonium derivatives is given by Smith and Bourns.[96]

Other β-deuterium isotope effect studies of β-phenethyl derivatives which appear to react by central *E*2 mechanisms include those of Burton and de la Mare on 1,1,2,3,4-pentachlorotetralin[97] (their α-deuterium isotope effect measurements provide additional support for a central mechanism where α-C has considerable sp^2 character), Willi on various 2,2-diphenethyl benzenesulphonates,[98] Bethell and Cockerill on 9-bromo-9,9′-bifluorenyl,[99] and Shiner

[93] B. D. England and D. J. McLennan, *J. Chem. Soc.* (*B*), 1966, 696.
[94] Y. Yano and S. Oae, *Tetrahedron*, 1970, **26**, 27.
[95] R. Baker and M. J. Spillett, *J. Chem. Soc.* (*B*), 1969, 481.
[96] P. J. Smith and A. N. Bourns, *Canad. J. Chem.*, 1970, **48**, 125.
[97] G. W. Burton and P. B. D. de la Mare, *J. Chem. Soc.* (*B*), 1970, 897.
[98] A. V. Willi, *J. Phys. Chem.*, 1966, **70**, 2705; *Helv. Chim. Acta*, 1966, **49**, 1725.
[99] D. Bethell and A. F. Cockerill, *J. Chem. Soc.* (*B*), 1969, 917.

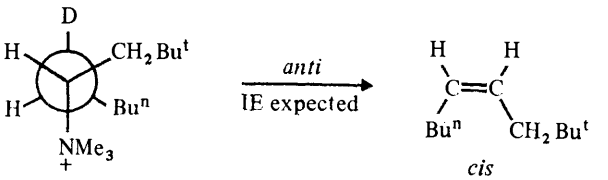
and De Puy and their co-workers on 2-aryl-1-propyl derivatives.[100]

Bunnett, Davis, and Tanida have reported[101] low (k^H/k^D = 2·4 and 2·6) β-deuterium isotope effects for the EtSNa- and MeONa-catalysed elimination reactions of 1-phenyl-2-methyl-2-chloro[1,1-$^2H_2$]propane, (10; Z = R^1 = H, R^2 = Me, X = Cl). They interpret these results in terms of a carbonium-ion-like *E*2 reaction. Presumably the β-hydrogen is less than half transferred from β-C to Y in the activated complex. It would be of interest to examine β-deuterium and leaving group X isotope effects as a function of changing substituent Z in such a system. As Z becomes more electron withdrawing the mechanism would probably move toward the central *E*2 area, resulting in increasing β-deuterium and decreasing X isotope effects.

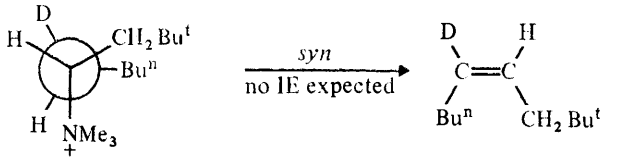
C. Isotope Effects in Other *E*2 Systems—*syn vs. anti* Elimination.—Almost all of the isotope-effect research in the β-phenethyl system has involved measurements of leaving group and β-deuterium effects. The possibilities for obtaining useful mechanistic data from α-C or β-C labelled compounds have not been exploited and there are not enough reported results on other systems to provide a solid base for mechanistic conclusions or extrapolation. Simon and Mullhofer[12] found little variation in isotope effects for elimination reactions of α-C carbon-14 labelled ethyl-, n-propyl-, and t-butyl-trimethylammonium salts ($k^{12}/k^{14} \sim$ 1·06—1·07 at 40 °C). Their value for α-C carbon-14 labelled 2-(*p*-nitrophenyl)-ethyltrimethylammonium salt decomposition was significantly lower, k^{12}/k^{14} = 1·026 at 100 °C, but as mentioned above, Hodnett and Dunn's value for the same effect at the same temperature was 1·078.[54] The discrepancy has not been resolved. Generally, these reactions all appear to have activated complexes with a good deal of carbanion character, implying relatively little $^{\alpha}$C—X bond weakening. All of the reported α-C-isotope effects seem quite high for such an activated-complex model. More extensive data are clearly needed. In the only β-C labelled isotope effect study reported, Simon and Mullhofer[12] found k^{12}/k^{14} = 1·036 for the decomposition of n-propyltrimethylammonium salts at 51 °C. Again, comparative data for other compounds would be very useful.

Shiner's initial report[25] of a large primary β-deuterium isotope effect, k^H/k^D = 6·7 at 25 °C, in the *E*2 elimination reaction of isopropyl bromide in ethanol–sodium ethoxide made it clear that the presence of an isotope effect could be diagnostic of mechanism. In recent years, this presence or absence of a primary β-deuterium isotope effect has been used extensively to help decide whether elimination in an *E*2 reaction takes place by a *syn* or an *anti* mechanism. For instance, in the decomposition of the *threo* quaternary ammonium salt (11a and d), large β-deuterium isotope effects were found by Pankova, Sicher, and Zavada[102] for both *cis*- and *trans*-olefin formation. For the isomeric *erythro*-

[100] V. J. Shiner, jun., and B. Martin, *Pure Appl. Chem.*, 1964, **8**, 371; V. J. Shiner, jun., and M. L. Smith, *J. Amer. Chem. Soc.*, 1961, **83**, 593; C. H. De Puy, D. L. Storm, J. T. Frey, and C. G. Naylor, *J. Org. Chem.*, 1970, **35**, 2746.
[101] J. F. Bunnett, G. T. Davis, and H. Tanida, *J. Amer. Chem. Soc.*, 1962, **84**, 1606.
[102] M. Pankova, J. Sicher, and J. Zavada, *Chem. Comm.*, 1967, 394

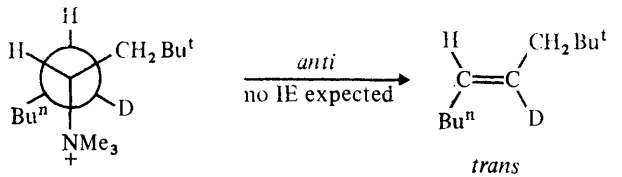


(11a)

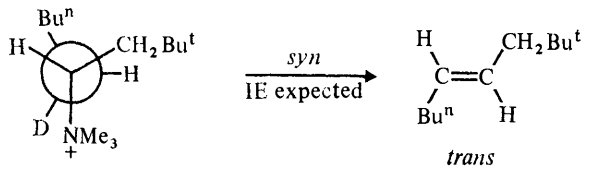


(11b)

$(k^H/k^D)_{cis} = 3{\cdot}1 - 4{\cdot}7$, *i.e. cis*-olefin is formed by *anti* elimination



(11c)



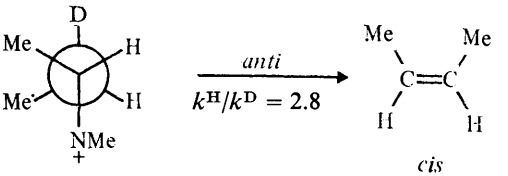
(11d)

$(k^H/k^D)_{trans} = 2{\cdot}3 - 4{\cdot}2$, *i.e. trans*-olefin is formed by *syn* elimination

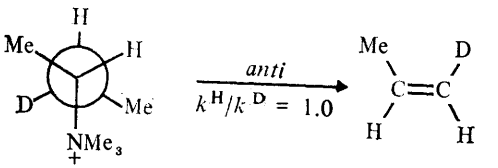
compound (11b and c), no isotope effect was found in the formation of either the *cis*- or *trans*-olefin. Clearly, the *cis*-olefin is being formed by the 'normal' *anti* elimination mechanism, whereas the *trans*-olefin is being formed by *syn* elimin-

ation. Similar isotope-effect results had been obtained early by Zavada,Svoboda, and Sicher[103] in their study of the decomposition of cyclodecyl quaternary ammonium salts. Since that time, similar isotope-effect or tracer studies have led to identification of the *syn* elimination mechanism as an exclusive or important path for formation of *trans*-olefins in a number of other systems.[104–107]

On the other hand, the same isotope-effect tool has been used to show that the elimination reactions of *threo*-1-methyl-2-deuteriopropyltrimethyl-ammonium ion (12), to both *cis*- and *trans*-2-butene proceed by *anti* mechanisms.[108] Similarly, both *cis*- and *trans*-2-butene are formed from *erythro*-3-



(12a)



(12b)

deuterio-2-bromobutane by *anti* mechanisms, the *trans*-olefin giving k^H/k^D values of 3·4—4·6, and the *cis*-olefin giving k^H/k^D values of 1·0—1·1.[109] *erythro* and *threo*-3-deuterio-2-butyl tosylates also undergo *anti* elimination only.[110]

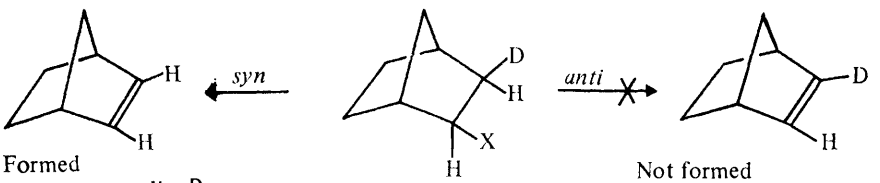
The remarkable difference in the mechanism of *trans*-olefin formation between quaternary ammonium salts (11) and (12) is almost certainly due to the differences in the steric environment about the β-hydrogen being removed in the elimination reaction.[105] Staggered conformations (11a) and (12a) give *cis*-olefin by normal *anti* elimination mechanisms; conformation (11b) is much more

[103] J. Zavada, M. Svoboda, and J. Sicher, *Tetrahedron Letters*, 1966, 1627;*Coll.Czech. Chem. Comm.*, 1968, **33**, 4027.
[104] J. L. Coke and M. C. Mourning, *J. Amer. Chem. Soc.*, 1968, **90**, 5561.
[105] D. S. Bailey and W. H. Saunders, jun., *Chem. Comm.*, 1968, 1598; *J. Amer. Chem. Soc.* 1970, **92**, 6904.
[106] M. Svoboda, J. Zavada, and J. Sicher, *Coll. Czech. Chem. Comm.*, 1967, **32**, 2104; 1968 **33**, 1415.
[107] M. Pankova, J. Zavada, and J. Sicher, *Chem. Comm.*, 1968, 1142; J. Zavada, M. Pankova, and J. Sicher, *ibid.*, 1968, 1145.
[108] D. H. Froemsdorf, H. R. Pinnick, jun., and S. Meyerson, *Chem. Comm.*, 1968, 1600.
[109] R. A. Bartsch, *Tetrahedron Letters*, 1970, 297.
[110] D. H. Froemsdorf, W. Dowd, and W. A. Gifford, *Chem. Comm.*, 1968, 449.

crowded. Conformation (12b) is relatively uncrowded, leading to normal *anti* elimination, but in its counterpart (11c) the large trimethylamino-group forces the carbon chains on both the α- and β-carbons back so as to 'surround' the *anti*-β-hydrogen, thus reducing its accessibility to the incoming base. In the alternate eclipsed conformation (11d) the β-hydrogen is 'surrounded' only on one side, and if the *alpha* and *beta* alkyl groups are large enough, this steric effect will overcome the natural tendency toward *anti* elimination through a staggered conformation. These steric effects should become worse as the complexity of (i) the α- and β-alkyl groups, and (ii) the base becomes greater, leading to a greater preference for the *syn* rather than the *anti* mechanism for *trans*-olefin formation. Bailey and Saunders[105] have found results corresponding to both such effects in their studies of the reactions of 2- and 3-hexyltrimethylammonium ions with various solvent–base systems.

Increased base strength also results in a greater tendency toward *syn* elimination.[105] All of these reactions seem to have a great deal of carbanion character; the very low nitrogen isotope effect, $k^{14}/k^{15} = 1{\cdot}002$, in the *syn* elimination of *trans*-2-phenylcyclohexyltrimethylammonium iodide[57] was cited earlier as evidence of this. Accordingly, it is quite likely that the β-hydrogen is more than half transferred from β-C to Y in all cases now being considered. Referring again to Figure 1, an increase in the base strength will cause the reaction to become even more carbanion-like, moving the activated complex even farther from the central B area toward H and G. This motion, being 'perpendicular' to the primary reaction co-ordinate, will cause even greater transfer of H from β-C to Y, thus reducing the isotope effect. An alternate view[105] is that increasing the base strength leads to less stretching of both the carbon–hydrogen and carbon–carbon bonds. In fact, the isotope effects for *syn* elimination, $k^H/k^D = 1{\cdot}9$—$2{\cdot}3$, seem to be smaller than those for *anti* elimination, $k^H/k^D = 2{\cdot}6$—$3{\cdot}4$, in almost all cases.[102,104,105]

In norbornyl and bicyclo[2,2,2]octyl derivatives, *syn* elimination is the predominant or exclusive path, as shown by deuterium tracer and isotope-effect studies.[111–113] In these compounds also, $(k^H/k^D)_{anti} > (k^H/k^D)_{syn}$.

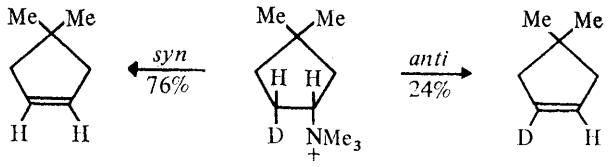


$k^H/k^D = 1{\cdot}86$

for $X = \overset{+}{N}Me_3$

[111] H. Kwart, T. Takeshita, and J. L. Nyce, *J. Amer. Chem. Soc.*, 1964, **86**, 2606.
[112] N. A. LeBel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Amer. Chem. Soc.*, 1963, **85**, 3199; N. A. LeBel, P. D. Beirne, and P. M. Subramanian, *ibid.*, 1964, **86**, 4144.
[113] J. L. Coke and M. P. Cooke, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 2779, 6701.

Coke and co-workers[114] have shown that *syn* elimination is an important (sometimes predominant) path for the Hofmann elimination in 4-, 5-, 6-, and 7-membered rings, where only *cis*-olefins can be formed. They used tracer and isotope effect techniques similar to those mentioned above. Brown and Saunders[115] extended the above research on 3,3-dimethylcyclopentyltrimethyl-



$k^H/k^D = 1{\cdot}71$ $\qquad$ $k^H/k^D = 1{\cdot}0$

ammonium salts to other base systems, and found that the amount of *syn* elimination varied widely (from 10% to 72% as the basicity of the medium increased). The values for k^H/k^D also varied somewhat with base (1·62—1·92) but no clear, mechanistically useful pattern is apparent. For cyclopentyltrimethylammonium ion, Brown and Saunders determined that $(k^H/k^D)_{anti} = 4{\cdot}75$ under conditions where $(k^H/k^D)_{syn} = 1{\cdot}85$ for the dimethylcyclopentyl compound.

Under conditions where only *anti* elimination is important, Saunders and Ashe[116] measured intramolecular β-deuterium isotope effects of $k^H/k^D = 4{\cdot}33$, 3·99, and 3·22 at 191 °C in aqueous base for cyclohexyl, cyclopentyl-, and 3-pentyl-trimethylammonium toluene-*p*-sulphonates. The results are interpreted in terms of increasing carbanionic character for the compounds in the order listed, resulting in increasing transfer of H from β-C to Y and thus decreasing values for k^H/k^D. Their stated plan to see if, as predicted, the nitrogen isotope effect will decrease in the order listed should provide a valuable test of these mechanistic ideas.

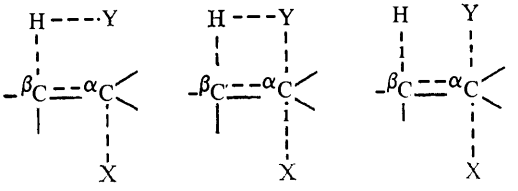
Finley and Saunders[27] have carried out an extensive study of primary β- and secondary α- and β-deuterium isotope effects in the *E*2 elimination reactions of cyclohexyl toluene-*p*-sulphonate in ethanol–sodium ethoxide and t-butyl alcohol–potassium t-butoxide. Both the α and β secondary isotope effects were large, $k^H/k^D = 1{\cdot}14$—1·15 and 1·36—1·51, and the primary β-effect was larger in t-butyl alcohol, $k^H/k^D = 7{\cdot}53$, than in ethanol, $k^H/k^D = 4{\cdot}47$. Although other interpretations of these data might be given, it is interesting to speculate that the activated complexes for these reactions might be near 'central' with much double bond character (near B in Figure 1). Both secondary isotope effects

[114] M. P. Cooke, jun., and J. L. Coke, *J. Amer. Chem. Soc.*, 1968, **90**, 5556; J. L. Coke and M. P. Cooke, jun., *Tetrahedron Letters*, 1968, 2253; J. L. Coke, M. P. Cooke, jun., and M. C. Mourning, *ibid.*, 1968, 2247.
[115] K. C. Brown and W. H. Saunders, jun., *J. Amer. Chem. Soc.*, 1970, **92**, 4292.
[116] W. H. Saunders, jun., and T. A. Ashe, *J. Amer. Chem. Soc.*, 1969, **91**, 4473.

are large, consistent with much sp^2 character for both α-C and β-C. If this were the case, the primary β-deuterium isotope effect in ethanol might correspond to slightly *less* than half transfer of H from β-C to Y. The result in t-butyl alcohol would then be shifted toward more carbanion character in the activated complex, corresponding to near symmetrical bonding of H to β-C and Y. It would be interesting to have primary and secondary β-deuterium isotope effect results for 1-methyl- or 1-phenyl-cyclohexyl toluene-*p*-sulphonate for comparative purposes. Such substitution should shift the activated complex toward the carbonium ion side of Figure 1.

6 Other Elimination Reactions and Mechanisms

A. Merged Elimination–Substitution Reaction Mechanisms.—The pioneering research of de la Mare and Vernon[117] demonstrated the greater effectiveness of the weaker base thiophenoxide ion than of the stronger base ethoxide ion in promoting elimination reactions. Since that time, elimination reactions have been shown to be induced with great facility by other weak bases, especially halide ions in dipolar aprotic solvents.[8,118–121] It is contended by some[8,121] that these reactions are more or less normal *E*2 eliminations, but the *E*2H–*E*2C spectrum of mechanisms proposed by Parker, Ruane, Biale, and Winstein[122] is supported by others, notably Parker's research group.[120] In the *E*2H–*E*2C proposal, removal of the β-hydrogen in elimination reactions is supposed to be accompanied by and aided to a greater or lesser extent by backside attack of Y on the $^{\alpha}$C—X bond, as shown in activated-complex models (13)—(15). To



(13) *E*2H (14) (15) *E*2C

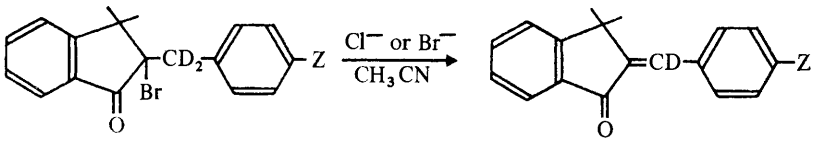
date, very little isotope effect research has been reported on reactions of this type, and it is not clear whether this mechanistic scheme can be distinguished

[117] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 1956, 41.
[118] S. Winstein, D. Darwish, and N. J. Holness, *J. Amer. Chem. Soc.*, 1956, **78**, 2915.
[119] R. A. Bartsch, *J. Org. Chem.*, 1970, **35**, 1023, and earlier work cited there.
[120] G. Biale, A. J. Parker, S. C. Smith, I. D. R. Stevens, and S. Winstein, *J. Amer. Chem. Soc.*, 1970, **92**, 115; D. Cook and A. J. Parker, *Tetrahedron Letters*, 1969, 4901, and earlier work cited there.
[121] J. F. Bunnett and E. Baciocchi, *J. Org. Chem.*, 1970, **35**, 76; D. Eck and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1969, **91**, 3099, and earlier work cited there.
[122] A. J. Parker, M. Ruane, G. Biale, and S. Winstein, *Tetrahedron Letters*, 1968, 2113.

from the usual *E*2 spectrum of mechanisms (Figure 1 above) on the basis of isotope effect measurements. It would appear that there is little if any difference between (13) and a 'central' or 'carbanion-like' *E*2 activated complex. For (14) and (15), the obvious difference from the *E*2 counterparts is in the interaction of Y with α-C. To the extent that this interaction is important, the α-C and secondary α-deuterium isotope effects should be shifted away from those characteristic of a carbonium-ion-like activated complex toward those characteristic of S_N2 reactions, that is toward higher α-C, and lower secondary α-deuterium isotope effects (see the analysis in the *E*1 section above). To the extent that this Y—$^{\alpha}$C interaction is not important, the mechanisms become part of the normal spectrum of *E*2 mechanisms. No α-C or α-deuterium isotope effect studies have been reported for these systems. There is some question in the author's mind as to whether such results would be considered to be useful by the proponents of the scheme since Parker's group contends[120] that in the *E*2C activated complex, β-C is virtually sp^2 hybridized and there is a well developed double bond between α-C and β-C.' It seems that two substituents and a well developed double bond at α-C leave little room for bonding between α-C and Y (or X).

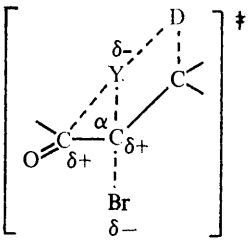
The small to medium-sized β-deuterium isotope effects in such reactions seem to be more or less normal for *E*2 reactions which are carbonium-ion-like *and* product-like (near F on Figure 1), where H is more than half transferred from β-C to Y^-. An *E*2 reaction with an activated complex between B and E in Figure 1, with the transfer of H from β-C to Y^- *less* than half complete, would also be consistent with the data. Comparative studies on structurally similar substrates would be needed for distinction. In the tetraethylammonium fluoride catalysed elimination reaction of β-phenethyl chloride,[123] the β-deuterium isotope effect was $k^H/k^D = 3{\cdot}99$ at 25 °C. The corresponding value for the tetraethylammonium chloride catalysed elimination reaction of t-butyl chloride in acetonitrile at 45 °C was $k^H/k^D = 3{\cdot}81$.[124] It is also easy to visualize an activated complex in the *E*2H–*E*2C spectrum which would be expected to give such results. More O'Ferrall has made a few model isotope effect calculations for such systems.[31]

Kevill, Cromwell, and co-workers[125] proposed a somewhat different kind of S_N–*E* merged mechanism for the halide-ion-promoted elimination of 2-bromo-2-benzyl-1-indanone and its 3,3-dimethyl derivative in acetonitrile. In their scheme, attacking nucleophile Y^- is oriented near the back side of the $^{\alpha}$C—X bond by



[123] J. Hayami, N. Ono, and A. Kaji, *Tetrahedron Letters*, 1970, 2727.
[124] D. N. Kevill and J. E. Dorsey, *J. Org. Chem.*, 1969, **34**, 1985.
[125] D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Amer. Chem. Soc.*, 1966, **83**, 4489, and earlier papers in the series cited there.

association with the nearby relatively positive carbonyl carbon. β-Deuterium isotope effects for the two compounds were k^H/k^D = 3·3 and 2·5 at 74 °C.



These results are consistent with an activated complex which is very carbonium-ion-like so that there is little weakening of the $^{\beta}$C—H bond and a low isotope effect. Introduction of the two methyl groups enhances the carbonium ion nature of the reaction (movement of the activated complex further toward E from B on Figure 1), reducing the transfer of H from β-C to Y, and reducing the isotope effect. Although such measurements have not been made, if this is the correct interpretation of the mechanism of the reaction, it would be predicted that the α-C isotope effect would decrease and the X isotope effect would increase when the two methyl groups are introduced. Another interesting consequence of this mechanism is that an isotope effect would be expected for the carbonyl carbon carbon-14 labelled compound. (But since the developing double bond is conjugated with the carbonyl group in any mechanism, at least a kind of secondary carbon-14 isotope effect for the carbonyl carbon labelled compound might be expected.) The Hammett plot of the rate data for various Z groups is curved, indicating a mechanism changing with Z. It would be interesting to see if there are corresponding changes in k^H/k^D, *etc.*

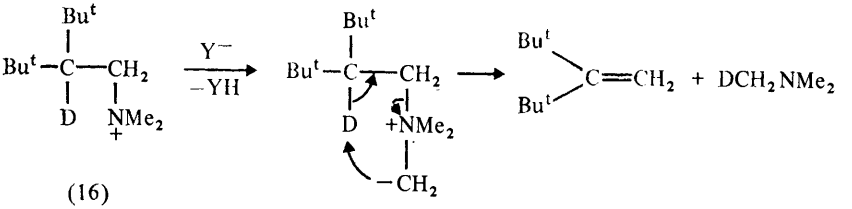
A third type of merging of substitution and elimination reaction mechanisms has been proposed by Sneen and Robbins,[126] but no attempt has been made as yet to study its isotope effect ramifications.

The iodide-promoted elimination of bromine from 1,1,2,2-tetrabromo[1,2-$^2H_2$]-ethane may also have a *S–E* merged mechanism of some sort. Lee and Miller observed[127] a secondary deuterium isotope effect of $k^H/k^D \cong 1{\cdot}28$ at 81—111 °C, which is consistent with considerable double bond character in the activated complex.

B. The Ylide Mechanism.—The ylide mechanism for the decomposition of quaternary ammonium salts and related compounds is a special case of the carbanion mechanism, and much of the isotope effect discussion in the *E*1cb section above is pertinent to the ylide case as well. Cope and Mehta[128] showed that quaternary

[126] R. A. Sneen and H. M. Robbins, *J. Amer. Chem. Soc.*, 1969, **91**, 3100.
[127] W. G. Lee and S. I. Miller, *J. Phys. Chem.*, 1962, **66**, 655; see also C. S. T. Lee, I. M. Mathai, and S. I. Miller, *J. Amer. Chem. Soc.*, 1970, **92**, 4602.
[128] A. C. Cope and A. S. Mehta, *J. Amer. Chem. Soc.*, 1963, **85**, 1949.

ammonium hydroxide (16) decomposed to 1,1-di-t-butylethylene with nearly complete transfer of the β-deuterium atom to the trimethylamine evolved, indicating predominant reaction through ylide (17). No methyl-deuterium or



(16) (17)

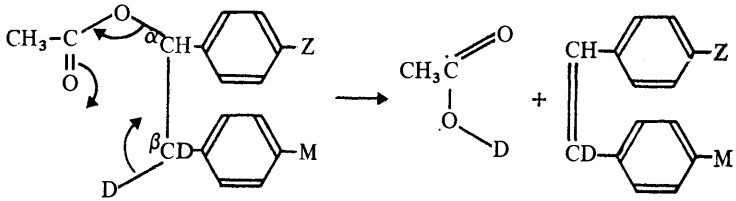
methyl-carbon-14 isotope effect studies appear to have been carried out on such reactions. Isotope effects would be expected for such labelled compounds, subject to the usual carbanion isotope effect considerations (see the *E*1cb section above), and for the nitrogen, $^{\alpha}$C, $^{\beta}$C, and α- and β-hydrogen labelled compounds as well, if conversion of (17) to olefin is rate determining. On the other hand, if formation of (17) is rate determining, no isotope effects would be expected for the nitrogen, α-C, β-C, or α- or β-hydrogen labelled compounds.

Using the tracer technique illustrated above, the ylide mechanism has been excluded for a number of elimination reactions.[57,100,102,105,113,129]

In the decomposition of 5α-cholestan-6β-yl trimethylammonium iodide and its tris-trideuteriomethyl isotopic isomer in ethanol at 70 °C, Cooper and McKenna[130] found k^{H}/k^{D} = 1·6. The authors suggest that this high 'secondary' isotope effect has a steric origin, in that there is more steric compression to be relieved in the unlabelled than the labelled compound. It is interesting to speculate about the possible alternative explanation that the reaction might be proceeding, at least in part, by an iodide ion-promoted ylide mechanism with an accompanying primary isotope effect.

C. Pyrolytic Elimination Reactions.[131]—Several β-deuterium isotope effect studies of *syn* eliminations in the pyrolyses of esters have been reported.[132] In all cases the k^{H}/k^{D} values are quite large, and the results are interpreted in terms of a concerted reaction involving a six-membered cyclic activated complex in which there is considerable $^{\beta}$C—H bond rupture. No systematic comparisons of k^{H}/k^{D} values for closely related compounds have been carried out, nor have isotope effects been measured for any α-C or β-C labelled com-

[129] W. H. Saunders, jun., and D. Pavlovic, *Chem. Ind. (London)*, 1962, 180.
[130] G. H. Cooper and J. McKenna, *Chem. Comm.*, 1966, 734.
[131] C. H. DePuy and R. W. King, *Chem. Rev.*, 1960, **60**, 431; A. Maccoll, 'Olefin-forming Eliminations in the Gas Phase', in 'The Chemistry of Alkenes', ed. S. Patai, Interscience Publishers, New York, 1964, p. 203.
[132] D. Y. Curtin and D. B. Kellom, *J. Amer. Chem. Soc.*, 1953, **75**, 6011; P. S. Skell and W. L. Hall, *ibid.*, 1964, **86**, 1557; C. H. DePuy, R. W. King, and D. H. Froemsdorf, *Tetrahedron*, 1959, **7**, 123; A. T. Blades and P. W. Gilderson, *Canad. J. Chem.*, 1960, **38**, 1401, 1407, 1412.

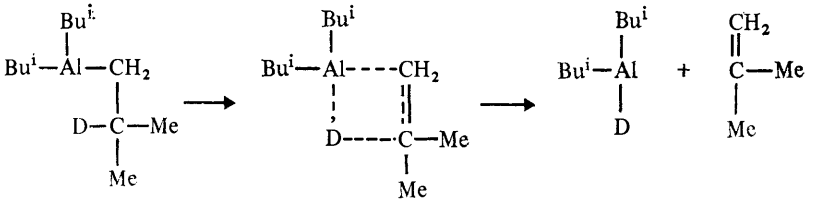


(18)

pounds. Considerable kinetic information is available[133] on system (18), and it would be interesting to examine the primary isotope effects for α-C, β-C, and β-hydrogen labelled compounds as a function of Z and M. Similar secondary isotope effect studies with the α-hydrogen labelled compounds would also be of interest.

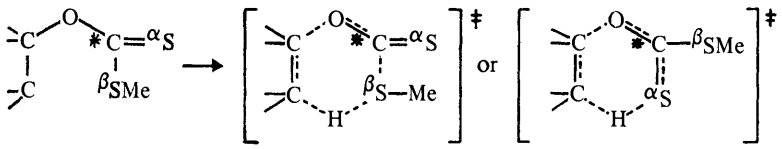
Blades, Gilderson, and Wallbridge[134] have also observed large deuterium isotope effects in the thermal elimination reactions of ethyl chloride and bromide. The results are interpreted in terms of a four-centre activated complex with considerable $^{\beta}$C—H bond rupture. Studies of the variation of carbon, halogen, and deuterium isotope effects in the corresponding thermal decompositions of a series of *p*-substituted α- and/or β-phenethyl halides would be of interest.

In a recent study of a rather unusual reaction, Egger[135] measured the β-deuterium isotope effect in the thermal decomposition of 2-deuteriotri-isobutyl-aluminium. The isotope effect is large, $k^{H}/k^{D} = 3{\cdot}7$ (extrapolated to 25 °C from higher temperature data), and is interpreted in terms of a four-membered cyclic activated complex.



The isotope effect study of the Chugaev reaction by Bader and Bourns[136] is a classic example of the use of the successive labelling approach. They were able to distinguish between two suggested *syn* elimination mechanisms, represented by activated complexes (19) and (20), for the pyrolysis of 5-methyl-*trans*-2-methyl-1-indanyl xanthate on the basis of *C, α-S and β-S isotope effect

[133] G. G. Smith, F. D. Bagley, and R. Taylor, *J. Amer. Chem. Soc.*, 1961, **84**, 3647; R. Taylor, *J. Chem. Soc.*, 1962, 4881.
[134] A. T. Blades, P. W. Gilderson, and M. G. H. Wallbridge, *Canad. J. Chem.*, 1962, **40**, 1526, 1533; A. T. Blades, *ibid.*, 1958, **36**, 1043.
[135] K. W. Egger, *Internat. J. Chem. Kinetics*, 1969, **1**, 459.
[136] R. F. W. Bader and A. N. Bourns, *Canad. J. Chem.*, 1961, **39**, 348.

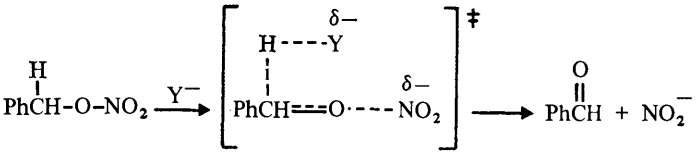


(19) (20)

studies. The observed *C, α-S, and β-S isotope effects were $k^{12}/k^{13} = 1{\cdot}0004 \pm 0{\cdot}0006$, $1{\cdot}0086 \pm 0{\cdot}0016$, and $1{\cdot}0021 \pm 0{\cdot}0007$. These values are consistent with a large bonding change at α-S, a small bonding change at β-S, and little or no total bonding change at *C, in going from reactant to activated complex. Inspection of (19) and (20) clearly reveals the superiority of the latter, especially as far as the α-S isotope effect is concerned. The size of the β-S isotope effect is a bit disturbing for reaction through (20); perhaps there is also considerable *C—βS bond stretching at the saddle point (that bond must eventually break in forming the final products).

In related work, Briggs and Djerassi found[137] the expected normal β-deuterium isotope effects in the *syn* elimination reactions of 2-methylcyclohexyl-*S*-methyl xanthates and acetates. However, some *anti* elimination was also found and, for the xanthates, this reaction proceeded without any detectable β-deuterium isotope effect. The authors interpreted this unusual result in terms of an *E*1 type reaction, where αC—O bond rupture, unassisted by β-hydrogen bond extension, was the rate-determining step. For the *anti* elimination of the acetate, the β-deuterium isotope effect found was interpreted in terms of a similar carbonium-ion-like activated complex but, in this case, with neighbouring hydrogen assistance.

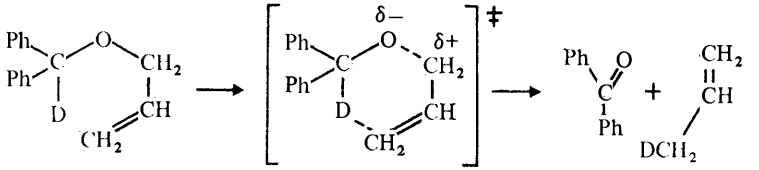
D. Eliminations to Form Carbon–Oxygen and Carbon–Sulphur Double Bonds.— Several isotope effect studies have been carried out on elimination reactions which result in the formation of carbonyl or thiocarbonyl groups or of sulphenes. The experimental approaches, mechanistic tests and conclusions, and general results are much the same as in olefin-forming eliminations. Buncel and Bourns[138] found a large nitrogen isotope effect, $k^{14}/k^{15} = 1{\cdot}0196$ at 30 °C, in the conversion of benzyl nitrate to benzaldehyde in an ethanol–ethoxide ion system.



[137] W. S. Briggs and C. Djerassi, *J. Org. Chem.*, 1968, **33**, 1625.
[138] E. Buncel and A. N. Bourns, *Canad. J. Chem.*, 1960, **38**, 2457.

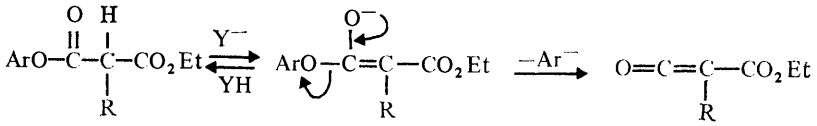
No deuterium was incorporated into the recovered reactant which was carried out in C_2H_5OD, so it is clear that a carbanion is not formed reversibly. The results are consistent with an *E*2-like concerted elimination. In a similar study, Smith and Bourns[139] found large nitrogen, $k^{14}/k^{15} = 1{\cdot}0091—1{\cdot}013$, and β-deuterium isotope effects, $k^H/k^D = 4{\cdot}25$, in the conversion of 9-fluorenyl nitrate to fluorenone, again consistent with a concerted *E*2-like mechanism.

A much smaller β-deuterium isotope effect, $k^H/k^D \cong 1{\cdot}1$ at 430 °C, was measured by Cookson and Wallis[140] in the pyrolysis of allyl diphenylmethyl ether to form benzophenone and propene. The low value was thought to be



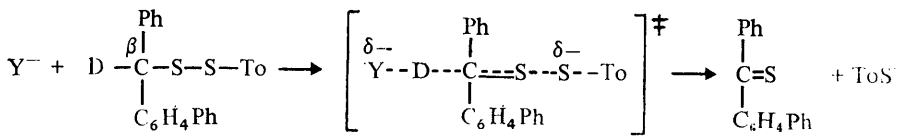
accounted for by an activated complex with much carbonium ion character at the allylic carbon and little stretching of the benzhydryl C—D bond. An excellent check on the mechanism of this reaction would be to measure carbon-14 isotope effects for compounds successively labelled at the benzhydryl carbon and the three carbons of the allyl group.

Malonic esters and related compounds containing easily cleaved —OAr groups may hydrolyse by carbonyl-forming elimination reactions to produce keten intermediates. Several solvent deuterium isotope effect studies[141] give



results consistent with a type B *E*1cb mechanism (reversible carbanion formation).

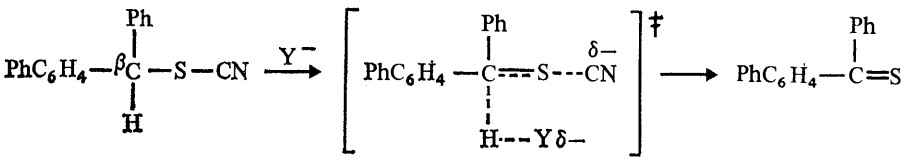
Thiocarbonyl groups are formed in elimination reactions of Ar—S^- from disulphides. The β-deuterium isotope effect for such an elimination reaction from α(biphenyl-4-yl)benzyl *p*-tolyl disulphide in isopropyl alcohol–sodium



[139] P. J. Smith and A. N. Bourns, *Canad. J. Chem.*, 1966, **44**, 2553.
[140] R. C. Cookson and S. R. Wallis, *J. Chem. Soc.* (*B*), 1966, 1245.
[141] For leading references, see R. F. Pratt and T. C. Bruice, *J. Amer. Chem. Soc.*, 1970, **92**, 5956.

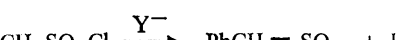
isopropoxide at 30 °C was found[142] to be large, k^H/k^D = 6·1, consistent with an activated complex with H about equally bonded to β-C and Y.

The corresponding elimination of HCN(DCN) from 4-phenyldiphenylmethyl



thiocyanate had a much smaller isotope effect,[143] k^H/k^D = 3·0, at 20 °C. This was interpreted in terms of greater transfer of H from β-C to Y in the activated complex than for the above disulphide case. Sulphur, β-C, and cyanide carbon isotope effect data would be helpful in further placing these reactions at their proper positions within their *E*2-like mechanistic spectrum.

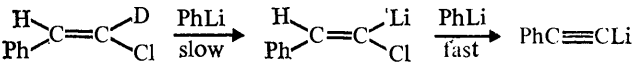
In related research, alkane sulphonyl chlorides were found to undergo base-catalysed elimination reactions to give sulphenes.[144] The β-deuterium isotope



effects were low, k^H/k^D = 2·0—4·0, consistent with extensive transfer of H from β-C to Y in the activated complex.

E. Elimination to Form Triple Bonds.—Several deuterium isotope effect studies have been carried out on elimination reactions of olefinic substrates, leading to the formation of acetylenic compounds. Prichard and Bothner-By[145] concluded that the elimination–rearrangement reaction of 1-bromo-2,2-diphenylethylene to diphenylacetylene takes place by a type B (pre-equilibrium) *E*1cb mechanism. The solvent isotope effect was k^H/k^D = 0·53, consistent with that conclusion (see the discussion in the *E*1cb section above).

In a rather unusual reaction, Schlosser and Ladenberger[146] found large, k^H/k^D ~ 7·3—15·3, α-deuterium isotope effects and small, k^H/k^D ~ 1·00—1·04, β-deuterium isotope effects in the dehydrochlorination of *cis*- and *trans*-1-chloro-2-phenyl styrenes with phenyl-lithium. The mechanism proposed for this reaction involves rate-determining abstraction of the α-hydrogen by the phenyl-lithium, followed by fast elimination of HCl from the lithium compound.

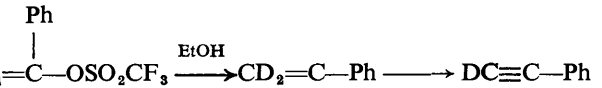


[142] U. Miotti, U. Tonellato, and A. Ceccon, *J. Chem. Soc.* (*B*), 1970, 325.
[143] A. Ceccon, U. Moitti, U. Tonellato, and M. Padovan, *J. Chem. Soc.* (*B*), 1969, 1084, and earlier papers in the series cited there.
[144] J. F. King and T. W. S. Lee, *J. Amer. Chem. Soc.*, 1969, **91**, 6524.
[145] J. G. Pritchard and A. A. Bothner-By, *J. Phys. Chem.*, 1960, **64**, 1271.
[146] M. Schlosser and V. Ladenberger, *Chem. Ber.*, 1967, **100**, 3877.

The isotope effect results are in accord with such a mechanism.

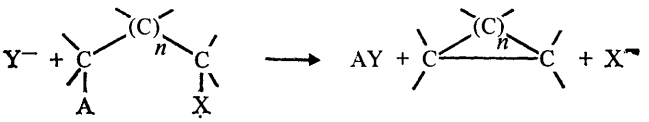
In the triethylamine-catalysed dehydrobromination of *cis*-[$^2H_2$]dibromoethylene to bromoacetylene, Kwok, Lee, and Miller[147] found no deuterium exchange with solvent, and no isotope effect, $k^H/k^D = 1{\cdot}00$. From their overall analysis of the reaction, they concluded that the reaction took place by an *E*1cb mechanism in which the R^- YH^+ ion pairs which were formed rapidly and reversibly did not dissociate before undergoing loss of bromide ion at an isotope independent rate to give products (see the discussion above in the *E*1cb section).

In contrast to the above carbanionic reactions, Hargrove, Dueber, and Stang[148] have shown that certain ethylenic compounds can also undergo *E*1 reactions to give acetylenes. In the solvolysis of β-styryl trifluoromethanesulphonate, the secondary β-deuterium isotope effect is $k^H/k^D = 1{\cdot}42$. Approximately 35% of the product was phenylacetylene, the remainder being acetophenone. The secondary isotope effect for this reaction is larger than the corresponding effect for *E*1–S_N1 reactions of saturated substrates. The authors suggest that this is because the developing *p*-orbital on α-C is exactly lined up with the $^\beta$C—H bond, making hyperconjugative delocalization of the developing positive charge especially effective; and that the $^\beta$C—H bond in this unsaturated system is closer to α-C and shorter than a corresponding saturated $^\beta$C—H bond.



No isotope effect studies of elimination reactions to form carbon–nitrogen triple bonds appear to have been carried out, but would be of interest.

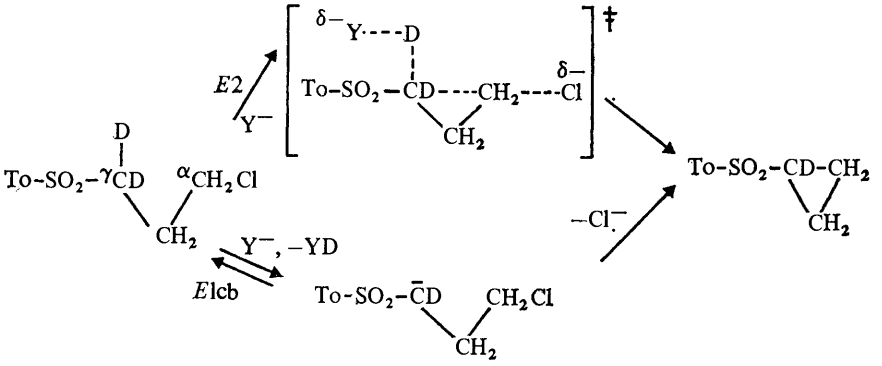
F. Eliminations to Form Cyclic Compounds.[149]—Most cyclization reactions might be classified as eliminations, and many isotope effect studies have been carried out on such systems. Such reactions are taken to be beyond the scope



of this review, but the general considerations of establishing whether a reaction is concerted or stepwise, and of determining the degree of bonding changes at various positions by isotope effect techniques are the same as those discussed here. Two examples will be considered.

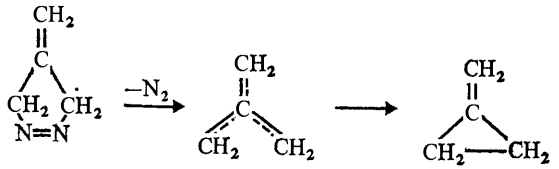
[147] W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, 1969, **91**, 468.
[148] R. J. Hargrove, T. E. Dueber, and P. J. Stang, *Chem. Comm.*, 1970, 1614.
[149] An interesting review of early work in one aspect of this field is given by V. Prelog, *Rec. Chem. Progr.*, 1957, **18**, 247.

In studying the cyclization of 3-chloro-1,1-dideuteriopropyl *p*-tolyl sulphone in Bu^tOD–$KOBu^t$, Bird and Stirling[150] found an inverse solvent isotope effect, $k^H/k^D = 0{\cdot}5$. The unlabelled substrate underwent rapid exchange of the γ-hydrogens with labelled solvent. These results are incompatible with an *E*2



mechanism, for which a larger, normal γ-deuterium isotope effect would be expected (using labelled substrate in labelled solvent); but they are completely consistent with a type B (pre-equilibrium) *E*1cb mechanism (see the detailed discussion of such systems in the *E*1cb section above).

Crawford and Cameron[151] concluded that the symmetrical trimethylenemethane (21) was an intermediate in the elimination of nitrogen from 4-methylene-1-pyrazoline to form methylene cyclopropane on the basis of isotope effect



(21)

studies. When the 3,3-dideuteriopyrazoline was used, more of the label was found in the ring than in the *exo*-methylene group, indicating an intramolecular isotope effect ($k^H/k^D = 1{\cdot}37$) in the conversion of (21) to product. When combined with the data on decomposition of the 3,3-dideuterio-*exo*-dideuteriopyrazoline, this result led the authors to conclude that (21) was indeed an intermediate, and that an alternative concerted mechanism for product formation was excluded. An important contribution to the observed large secondary isotope effect was thought to be the greater ponderal effect for rotation of CD_2 than of CH_2.

[150] R. Bird and C. J. M. Stirling, *J. Chem. Soc.* (*B*), 1968, 111.
[151] R. J. Crawford and D. M. Cameron, *J. Amer. Chem. Soc.*, 1966, **88**, 2589.

G. α-Elimination Reactions.—Isotope effect studies have been carried out on numerous reactions involving carbene or carbenoid intermediates, and many of these reactions can be classified as α-eliminations. Most such research is considered to be beyond the scope of this review, but, as before, isotope effect data can provide valuable mechanistic information.[152] Two examples will be discussed briefly. Skell and Plonka[153] generated carbene (22) by co-condensing carbon vapour and the labelled acetone on to a liquid nitrogen cooled surface under high vacuum. The intramolecular isotope effect in the conversion of (22) to propene was $k^H/k^D = 1{\cdot}7$ at −170 °C (estimated to be 1·1 at 25 °C). The authors take

$$CH_3COCD_3 + C \cdot \xrightarrow{-170°C} CO + CH_3-\ddot{C}-CD_3 \quad \begin{matrix} \xrightarrow{k_H} CH_2{=}CH{-}CD_3 \\ \xrightarrow{k_D} CH_3{-}CD{=}CD_2 \end{matrix}$$

(22)

the low value of k^H/k^D to indicate that a free carbene is involved, as contrasted with higher isotope effect values reported for complexed carbenes or carbenoid reactions.

Swain and Thornton have reported[154] a sulphur isotope effect of $k^{32}/k^{34} = 1{\cdot}0066$ in the hydroxide ion catalysed conversion of *p*-nitrobenzyldimethylsulphonium toluene-*p*-sulphonate to *pp'*-dinitrostilbene. The reaction was first-order with respect to hydroxide ion and the sulphonium salt, and

$$ArCH_2\overset{+}{S}Me_2 \underset{\text{fast}}{\overset{OH^-}{\rightleftharpoons}} Ar\ddot{\underset{-}{C}}H\overset{+}{S}Me_2 \xrightarrow{\text{slow}} Ar\ddot{C}H + Me_2S$$

(23)

$$Ar\ddot{C}H + (23) \xrightarrow{\text{fast}} R\ddot{C}HCH\overset{+}{S}Me_2 \xrightarrow{\text{fast}} ArCH{=}CHAr + Me_2S$$

(Ar)

carbanion (23) was formed reversibly as shown by deuterium exchange. A large sulphur isotope effect ($k^{32}/k^{34} \sim 1{\cdot}018$) would be expected for conversion of (23) to the carbene, so the cogent argument is made (indirectly) that the lower observed value must require an additional dimethyl-sulphide-producing step which proceeds without an isotope effect. The last step in the indicated mechanism provides such a path, since the second dimethyl sulphide will have the same isotopic composition as the then existing reactive intermediate[11] (23)

[152] For a few such applications, see H. Kwart and H. G. Ling, *Chem. Comm.*, 1969, 302; W. Kirmse, H. D. von Scholz, and H. Arold, *Annalen*, 1968, **711**, 22; J. R. Jones, *Trans. Faraday Soc.*, 1965, **61**, 95; S. Seltzer, *J. Amer. Chem. Soc.*, 1961, **83**, 2625; J. Hine, R. J. Rosscup, and D. C. Duffey, *ibid.*, 1960, **82**, 6120.
[153] P. S. Skell and J. H. Plonka, *Tetrahedron Letters*, 1970, 2603.
[154] C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, 1961, **83**, 4033.

(which will be somewhat enriched in the heavy isotope, but which will not show further fractionation in the last step). The isotopic composition of the measured dimethyl sulphide will be the average of that formed in the rate-determining and last steps.

The kind hospitality of Professor de la Mare and his colleagues during the author's visit at the University of Auckland, where this review was initiated, is gratefully acknowledged.